STUDIES IN THE CYCLOHEPTANE FIELD

THESIS

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by

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EXPERIMENTAL PROCEDURES

The infra-red measurements quoted were recorded on a Perkin-Elmer 137 spectrophotometer, in the case of spectra run on liquid films or in Nujol, and on a Unicam SP200 spectrophotometer, for solution and potassium chloride disc spectra.

Measurements of ultra-violet absorption spectra were made in ethanolic solution on a Perkin-Elmer 137UV spectrophotometer or on a Unicam SP500 spectrophotometer.

Nuclear magnetic resonance spectra were recorded on the Associated Electrical Industries (A.E.I.) RS2 instrument, using tetramethylsilane as internal reference standard. Melting-points were determined on a Kofler block. Vapour-phase chromatography was carried out on a Pye-Argon unit, on columns of 5% Apiezon 'L'.

Unless otherwise stated, all extracts of acidic aqueous media were washed with saturated sodium hydrogen carbonate, water, and dried over magnesium sulphate.

SUMMARY OF Ph.D. THESIS

IAN WILLIAM JAMES STILL

STUDIES IN THE CYCLOHEPTANE FIELD

In Section I, some of the reactions of tropilidene (or cycloheptatriene) are described. Attempts to convert tropilidene directly into tropone, or the so far unknown tropyl alcohol, by employing a variety of common oxidative procedures, have been unsuccessful. Active manganese dioxide, sodium dichromate, and performic acid all led to the formation of benzaldehyde in varying amounts. Attempts to epoxidize tropilidene, using monoperphthalic, perbenzoic, and performic acids, have likewise met with no success.

The latter part of Section I deals with the evidence obtained for the structures of the previously described bromine and hydrogen bromide addition products of tropilidene. In both cases it seems likely that a 1,2-addition mechanism is involved. Attempts to prepare hypobromous acid and ethyl hypobromite addition products were not successful — considerable amounts of benzaldehyde being produced in each case.

In Section IIa, synthetic work is described, which establishes the nature of the dehydration product of 2-hydroxy-2,6,6-trimethylcyclohept-4-en-1-one. This hydroxy-ketone was obtained previously as a product of the selenium dioxide oxidation of α-dihydroeucarvone. Ring-contraction occurs on dehydration with the formation of 1-acetyl-5,5-dimethylcyclohexa-1,3-diene. This ketone

has been synthesized from 5,5-dimethylcyclohexan-1,3-dione (dimedone), while its tetrahydro-derivative, 1-acetyl-3,3-dimethylcyclohexane, has also been synthesized from 3-methylcyclohex-2-en-1-one.

A number of oxidative degradations are also described in Section IIa, with a view to establishing the position of the double bond in α-dihydroeucarvone. These experiments were inconclusive, but the results of isomerizations to the conjugated β-dihydroeucarvone, in conjunction with the evidence obtained by vapour phase chromatography, indicated that α-dihydroeucarvone is in fact a mixture containing 75% of the γδ-unsaturated ketone, and 25% of the βγ-unsaturated ketone. This conclusion is confirmed by the nuclear magnetic resonance data.

A dimeric product, or mixture of products, obtained by the action of alkali on eucarvone is briefly described.

In Section IIb, the conversions of eucarvone into carenedione, and eucarvone trityl enol-ether are described. Various attempts to oxidize these bicyclic derivatives, with a view to the synthesis of the naturally occurring monoterpene, chamic acid, were unsuccessful.

Oximino-eucarvone, or carenedione monoxime, was converted to the corresponding diazo-ketone, which underwent thermal isomerization in the presence of air to yield carenedione. No useful results were obtained from attempted Beckmann rearrangements of oximino-eucarvone, but this compound yielded interesting iso-oxazoline rearrangement products on treatment with sulphuric acid. The structures of

these products have been fully elucidated by hydrogenolytic cleavage to known derivatives of carvacrol. Some interesting features of the ultra-violet absorption spectra of the rearrangement products and their derivatives are discussed.

Finally, the action of hot dilute acid on carenedione has afforded a rearrangement product, which may be a mixture of two hydroquinone derivatives. The evidence so far obtained for the two structures is discussed. The irradiation of carenedione yielded what appeared to be a hydroxy-lactone, but very little evidence has been obtained for its structure.

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SECTION 1

Some Reactions of Tropilidene

SECTION II

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SECTION I.

SOME REACTIONS OF TROPILIDENE

HISTORICAL INTRODUCTION

The interesting unsaturated hydrocarbon tropilidene (or cycloheptatriene) (1), was first obtained by Ladenburg[1], as a degradation product of the alkaloid tropine (2). The constitution of tropilidene was finally established by Willstätter[2] in 1898. Indeed, Willstätter, in his classical synthesis of tropidine (3)[3] from cycloheptanone, obtained tropilidene as an intermediate[3,4].

After these early researches, however, interest in tropilidene, which bears a formal similarity to benzene, lapsed completely. Indeed, little further work of any significance was carried out on the parent hydrocarbon until the years following 1950, which have seen a great upsurge of interest in the chemistry of seven-membered ring compounds. Possibly the most important single factor involved in this movement, was the reported preparation of tropylium bromide in 1954[5]. The existence of the tropylium (or tropenium) cation (4), which possesses a planar, six π-electron structure analogous to those of benzene (5) and cyclopentadienylide (6), was first postulated on theoretical grounds by E. Hückel[6] in 1931. The cation (4) had almost certainly been isolated, albeit unwittingly, by Merling[7] in 1891, as a degradation product of dibromo-tropilidene, although as stated above, its preparation and some of its unique properties were not reported until 1954, as a result of the work of Doering and Knox[5].

A second very important stimulus towards research in the field of cycloheptane derivatives lay in the discovery of two oxygenated, pseudo-aromatic compounds, tropone (7) and tropolone (8). The present discussion will, however, confine itself to a consideration of the purely hydrocarbon species, tropilidene and tropylium.

A variety of synthetic approaches to tropilidene and some of its alkyl-substituted derivatives has appeared in the chemical litterature of recent years. Some of the more general and more novel methods are described below.

The original method of Hofmann degradation of tropine (2) and related compounds is rather tedious, and is, of course, subject to limitations in the substitution pattern of the tertiary base. This method has been the subject of a recent comprehensive review[8].

The most common laboratory source of tropilidene and its derivatives, lies in the ring-expansion of aromatic compounds. Diazo-compounds have been widely used for this purpose, since Doering and Knox[9] first prepared tropilidene by the irradiation of diazomethane in benzene. The same authors also revealed the generality of this method by preparing various alkyl- and aryl-substituted tropilidenes from the corresponding benzene derivatives[10]. Some German workers[11] have recently claimed almost quantitative yields for the conversion of benzene to tropilidene by simply refluxing diazomethane in benzene in the presence of cuprous chloride or bromide. By employing ethyl diazo-acetate,

it is possible by similar means to obtain various carboxylic acid derivatives of tropilidene.[12, 13,14.] A similar type of ring-expansion, involving the reaction of benzene with methylene chloride and methyllithium, and proceeding by addition of the resulting chlorocarbene to form the intermediate norcaradiene (9), (X=Cl), yields as the final product 7-methylcyclohepta-1,3,5-triene (10)[15].

Other types of ring-expansion, involving Wagner-Meerwein rearrangements, have recently been studied. Bicyclo (3:2:0) hept-2-en-6-one (11) was reduced to the corresponding alcohol, which formed a methanesulphonyl derivative (12). Solvolysis of (12) in buffered acetic acid gave tropilidene in good yield.[16] The reduction of benzoic acid using sodium in liquid ammonia gives rise to 1,4-dihydrobenzoic acid (13)[17]. Methylation of this acid affords (14) which is converted by reduction to the primary alcohol and solvolysis of the corresponding p-toluenesulphonyl derivative, into methyltropilidene (15)[18]. Again, this reaction may be applied to substituted benzoic acids, enabling a large number of alkyl-substituted tropilidenes to be prepared by this means.

There are very few reported instances of the converse process of ring-contraction of cyclooctane derivatives, but it is of interest to note that Ganellin and Pettit[19] have reported the isolation of 7-carboxy-tropilidene (16) from the reaction of cyclooctatetraene (17) with acidic permanganate, while Cope and his co-workers[20] claim to have prepared

7-formyltropilidene as its dimethyl acetal (18) by treating cyclooctatetraene with mercuric acetate in methanol.

On the industrial scale, tropilidene is prepared by the thermal isomerization of bicyclo(2:2:1) hepta-2,5-diene (19) at 400°[21]. Some Russian workers[22] claim to have obtained a mixture of tropilidene and bicyclo (2:2:1) hepta-2,5-diene by heating cyclopentadiene and acetylene under pressure.

The initial isolation of tropylium bromide described by Doering and Knox[5], involves the addition of 1 mole of bromine to tropilidene to give a liquid dibromide, possibly (20), which then loses hydrogen bromide on heating under vacuum to give tropylium bromide (4), (X = Br). The most general method of obtaining tropylium salts, however, involves hydride transfer from a tropilidene derivative to some suitable acceptor. Thus, tropilidene itself is converted by treatment with triphenylmethyl perchlorate or fluoborate in acetonitrile into the corresponding tropylium salts (4), ($X = Cl O_4$, BF_4), which are much more stable than the tropylium halides[23]. Tropilidene is converted into the stable stannichloride salt of tropylium (4), ($X = Sn Cl_5$) on treatment with a solution of stannic chloride in tert-butyl chloride[24]. Recent work on the effect of quinones, and in particular tetrachloro-1,2-benzoquinone (TBQ) (21) and 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) (22), upon tropilidene, has led to the preparation of a whole

series of tropylium salts, by allowing the oxidation to proceed in the presence of suitable anions[25].

Oxidative procedures, other than those involving hydride transfer, have been utilized to convert tropilidene into the tropylium ion. The anodic oxidation of tropilidene at a platinum electrode[26] ($C_7H_8 \longrightarrow H^+ + C_7H_7^+ + 2e$), and the oxidation of cycloheptа-1,3,5-triene-7-carboxylic acid (16) with a wide variety of oxidizing agents[27], come into this category. The latter oxidation involves an initial two-electron transfer, and such a mechanism is valid, where R forms a stable cation, as in the present case.

$$R\text{-}CO_2H \longrightarrow R^+ + CO_2H^+ + 2e.$$

Dewar and Ganellin[28] have also reported the isolation of tropylium bromide by treating the silver salt of the above acid with bromine (Hunsdiecker reaction), and tropylium perchlorate by decarbonylation of the acid chloride with silver perchlorate.

The detailed structure of tropilidene has received considerable attention. The choice of the monocyclic triene structure (1), in preference to the bicyclic formulation (9), (X = H), was largely as a result of the nuclear magnetic resonance study carried out by Corey and his co-workers.[29] They showed that the ratio of saturated to olefinic hydrogen atoms was 1:3, and not 1:1 as would arise from a bridged structure.

By contrasting the complexity of the NMR spectrum of the non-planar cyclooctatriene (23), and the resonance

energy value of 6-8 kcal. for the former, as compared with 2 kcal. for the latter, Doering and his collaborators[30] have postulated the planar, pseudo-aromatic structure (1a) for tropilidene. Evans and Lord[31] have recently produced evidence in support of this formulation, on the basis of a careful study of the Raman and infra-red spectra of tropilidene. Their results are not in complete accord with its formulation as cyclohepta-1,3,5-triene (1), and are best explained in terms of a molecule possessing a planar, quasi-aromatic ring of C_{2V} symmetry, although they do not exclude a structure in which the CH_2 group is displaced slightly from the molecular plane. Recent thermochemical findings[32] are also consistent with the formulation of tropilidene as (1a).

Conrow[33], however, has questioned the above findings as a result of his studies on the acid-catalyzed equilibrium between 2,3,7,7-tetramethylcyclohepta-1,3,5-triene (24), and 2-methylene-3,7,7-trimethylcyclohepta-3,5-diene (25). On this basis, and by making due allowance for the stabilization of (24) over (25) as a result of the olefinic bond involved in the isomerization being tri-substituted in (24) and di-substituted in (25), Conrow claims that the amount of 1,6-overlap in (24), or in tropilidene itself, is relatively small.

There have been relatively few papers to date, dealing with the chemical reactions of tropilidene, other than those which lead to the formation of tropylium salts. In 1953, Alder and Jacobs[34] reported the isolation of

an adduct with maleic anhydride, to which they assigned the structure (26) on the basis of a number of degradative experiments. Thus, in this case, tropilidene reacts as norcaradiene (9)$^{(X=H)}$, and it is of interest to note that tropone forms an adduct in which such valence tautomerism is not exhibited, since this would involve generating the unstable cyclopropanone system[35]. Tropilidene does not form a Diels-Alder type adduct with ethyl azo-dicarboxylate (27), the product (28) being derived simply by additive substitution at the C_7-position[36].

When treated with N-bromosuccinimide in the presence of a trace of benzoyl peroxide, the main product was shown to be N-cyclohepta-2,4,6-trienyl-succinimide (29)[37]. The preparation of aryl-derivatives of tropilidene by direct substitution has also been reported by Weiss and Lalande[38], as a result of the treatment of tropilidene with various diazotized aromatic amines under the conditions of the Meerwein reaction.

Reduction of tropilidene with sodium or lithium in liquid ammonia yields cyclohepta-1,3-diene, [39] while the addition of lithium alkyls gave 7-lithium-5-alkyl-cyclohepta-1,3-diene derivatives (30), which could then be hydrolyzed to the corresponding hydrocarbon, or converted to 5,7-dialkylcyclohepta-1,3-diene derivatives (31) by the use of alkyl halides[39].

Some Japanese workers[40] have obtained tropone in low yield by the selenium dioxide oxidation of tropilidene. Juppo and Wolf[41] have isolated benzaldehyde and benzoic

acid by oxidation with chromium trioxide. They showed by the use of ^{14}C-labelled tropilidene, that this oxidation must proceed by a salt of the symmetrical tropylium ion (4), ($X = OCrO_2OH$).

The photochemistry of tropilidene has been studied by Dauben and Cargill,[42] who have found that the valence tautomer, bicyclo(3:2:0)hepta-2,6-diene (32) is the sole product. Pyrolysis of this bicyclic compound causes reversal of the photochemical reaction and the formation of its seven-membered ring progenitor.

Experimental confirmation of the highly symmetrical structure of the tropylium cation has been derived from a study of its Raman and infra-red spectra.[43] The infra-red spectrum is particularly simple, exhibiting only four bands of reasonable intensity. The positions, distribution, and intensities of the seven Raman and the four infra-red bands are consistent only with a planar, aromatic structure analogous to benzene. This conclusion was recently confirmed by an elegant radio-chemical study carried out by a group of Russian workers[44], in which the equivalence of all seven carbon atoms in tropylium was fully established.

The properties of tropylium bromide were described in detail by Doering and Knox[5]. They found it to be a high-melting, strongly hygroscopic, water-soluble compound, which gave an instantaneous precipitate with aqueous silver nitrate, and could be catalytically hydrogenated to cycloheptane. In the basic medium, water, the tropylium ion behaves as a Lewis acid, which is in equilibrium with

the covalently bonded carbinol and a hydroxonium ion, i.e.

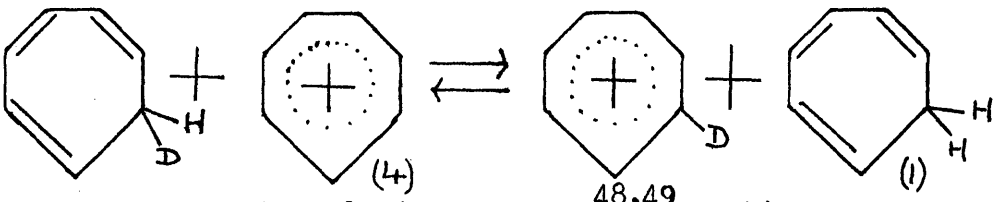
$$C_7H_7^+ + 2H_2O \rightleftharpoons (C_7H_7OH) + H_3O^+.$$

In fact, evaluation of the dissociation constant revealed that the tropylium ion is about as strongly acidic as acetic acid, with water as the reference base. In the same paper, Doering and Knox discovered that neutralization of tropylium bromide with sodium bicarbonate, gave ditropyl ether (33), instead of the expected carbinol (4), (X = OH) which has so far proved too unstable to permit its isolation.

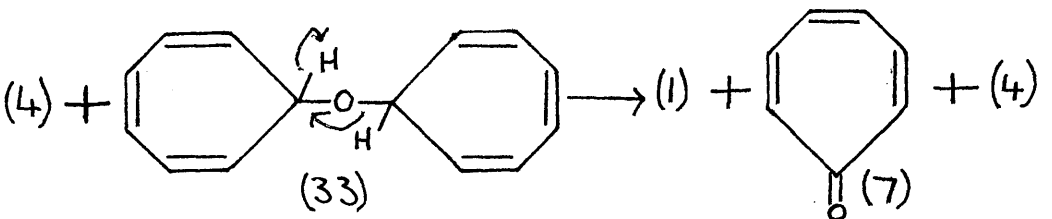
The nucleophilic character of the group X in tropylium compounds determines the degree of covalent bonding from X to the cation. Thus, when X = OMe, or CN, (4) no longer represents the structure of these compounds, which are typical covalent organic liquids. For the same reason, Doering and Knox[45] were unable to prepare the tropylium compounds in which X = OH, NH_2 or SH, since in each case these compounds reacted instantaneously with a second tropylium molecule to give the covalent ether, amine, and sulphide respectively (34) (B = O, NH,S). These reactions, and others of a similar nature, are discussed in a review of the tropylium ion by Doering and Krauch[46].

As previously mentioned under oxidation reactions of tropilidene, the tropylium ion is oxidized by chromium trioxide to benzaldehyde and benzoic acid. Reduction with zinc dust in aqueous media affords the dimeric hydrocarbon ditropyl (35)[45], by way of the relatively stable tropyl radical as intermediate. Tropylium readily abstracts

hydride ion from such reagents as lithium aluminium hydride or sodium borohydride, with the formation of tropilidene[47]. Indeed, the group of Russian workers who carried out these experiments have also shown, as a result of equilibration studies between monodeuterio-tropilidene and the tropylium ion, that this system represents the first reported instance of a truly reversible hydride transfer system:-



It has been shown by two groups,[48,49] working independently, that careful neutralization of a tropylium salt leads to the formation of tropilidene and tropone in approximately equal amounts. The rate-determining step is regarded as hydride transfer from the initially-formed ditropyl ether (33) to the tropylium ion as shown:-



As a final illustration of how the nucleophilicity of the group X in tropylium compounds influences the degree of covalent bonding from the group X to tropylium, it has been shown[50,51] that the ionic tropylium bromide (4), (X = Br) forms condensation products with active methylene compounds (e.g. (4), X = $CH_3CO.\dot{C}H.COO\,Et$), which are normal covalent compounds. Treatment of these derivatives, however,

with a strong acid like perchloric acid, causes a fragmentation reaction to occur,[52] with the formation of tropylium perchlorate and the regeneration of the active methylene compound.

DISCUSSION

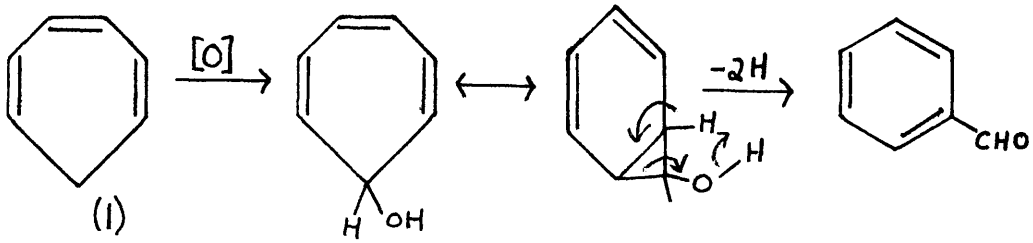
In view of the large number of interesting papers published in the last few years devoted to the fascinating pseudo-aromatic compounds tropone (7), tropolone (8), and the tropylium salts (4), it is perhaps not surprising that the parent hydrocarbon, tropilidene (or cycloheptatriene) (1), should have suffered some neglect as a consequence. We have undertaken to fill a few of the gaps in our knowledge of basic tropilidene chemistry by employing two broad classes of reaction. The first of these concerns attempts to introduce some oxygen-containing group directly into the tropilidene nucleus, particularly with a view to the preparation of tropone (7) and of tropolone (8), while the second has involved a study of some of the simpler electrophilic addition reactions which tropilidene might reasonably be expected to undergo.

In dealing first of all with the attempts to oxidize tropilidene, it must be conceded that no real progress has been made. The reasons for this are mainly that at ambient temperatures, tropilidene is quite stable towards a number of oxidants, while those reactions which have involved the use of rather higher temperatures have led frequently to over-oxidation, with the attendant production of intractable tars or complex mixtures. Furthermore, the action of an oxidizing agent on tropilidene in an acidic environment, has been found to lead, in almost every case investigated, to the formation of benzaldehyde and, in some cases, benzoic acid.

One of the first reagents to be tried was selenium dioxide, in various solvents including ethanol, dioxan, acetic anhydride, acetic acid, and mixtures of the last two. Since we observed no reaction with selenium dioxide at 25°, the temperatures employed were generally in the range 70-90°. In all cases, the production of selenium, both as a black precipitate, and in the red colloidal form, was evidence that some oxidation had occurred, but the products were very seriously contaminated with selenium, and revealed great complexity in the carbonyl region of their infra-red spectra. Attempts to isolate solid derivatives of tropone, such as the styphnic acid salt or the urea complex, from these mixtures were unavailing.

An attempt to introduce a hydroxyl or carbonyl group at the methylenic C_7-position in tropilidene was made using active manganese dioxide,[53] prepared by the pyrolysis of manganese carbonate. After prolonged shaking at 20°, large amounts of tropilidene were recovered, together with some benzaldehyde, identified as its 2:4-dinitrophenylhydrazone. On repeating the experiment with manganese dioxide, prepared in the same way, followed by washing with nitric acid and water to pH 4-5, the same result was observed, but the yield of benzaldehyde was now almost 50%. The mechanism of this reaction may well involve the intermediate tropylium hydroxide (X = OH), which has not as yet been isolated, although some Russian workers[54] claim to have isolated the corresponding acetate and benzoate as covalent compounds. The intermediate

is then farther oxidized, with rearrangement, to give benzaldehyde:-



By analogy with some successful oxidations carried out on cyclooctatetraene by Cope and his collaborators[20], using mercuric acetate, we have tried a number of similar experiments on tropilidene. No reaction was observed when the solvent employed was methanol, but in glacial acetic acid at 120° under nitrogen, the reaction mixture soon became dark green in colour, while mercury was deposited in almost theoretical amounts. Isolation and fractionation of the crude product revealed the presence of unreacted tropilidene and a higher-boiling acetate. The ultra-violet absorption spectrum of the acetate indicated the presence of a conjugated cyclo-heptadiene, which was possibly the diacetate (36), although no Diels-Alder adduct was obtained upon treatment with maleic anhydride. Treatment of a sample of the unsaturated acetate (36), with concentrated sulphuric acid in ethanol did not afford the deep blue colour which is characteristic of the norcaradiene structure (9).

When the mercuric acetate reaction was repeated, using a two-fold excess of the oxidant, a similar result was obtained. Treatment of the crude product with a methanolic hydrochloric acid solution of 2:4-dinitrophenylhydrazine

did give a solid derivative, but this was shown by ultra-violet spectroscopy to consist of not one, but several, 2:4-dinitrophenylhydrazones. At the same time, routine spot-tests revealed the presence of mercury in all fractions of the distillate from the original product. In view of the complex nature of the product, and the hazards involved in the handling of volatile mercury-containing substances, this series of experiments was terminated.

The reaction of tropilidene with lead tetraäcetate under conditions similar to those used in the conversion of toluene to benzyl acetate,[55] led to the formation of what was obviously a mixture of acetates. Solvolysis of the mixture with sodium in methanol gave rise to a mixture of hydroxy-compounds from which no carbonyl compound was obtained on prolonged treatment with manganese dioxide. Thus it would appear that the desired tropylium acetate (4), (X = OAc) was not among the original products.

An attempt to prepare tropylium benzoate (4), (X = OBz) by oxidation of tropilidene with tert-butyl perbenzoate, led to the formation of two distinct benzoate derivatives, as well as some benzoic acid, identified by melting-point, mixture melting-point, and infra-red. Neither of these benzoate derivatives yielded a satisfactory analysis for tropylium benzoate, although the presence of at least one benzoate grouping in each was verified by ultra-violet spectroscopy.

Tropilidene was rapidly oxidized by sodium dichromate in acetic acid to a mixture of benzaldehyde and benzoic acid[56].

An attempt to prepare the known tropone oxime was made by employing base-catalyzed nitrosation of tropilidene with iso-amyl nitrite. Large amounts of starting-material were recovered from this reaction, together with a dark red viscous oil from which no solid material could be isolated.

A number of attempts to epoxidize tropilidene have been made, using monoperphthalic acid, perbenzoic acid, and performic acid. When the hydrocarbon was allowed to react with monoperphthalic acid in ether at 20°, large quantities of phthalic acid were produced, but only unreacted tropilidene was recovered, irrespective of the molar proportions of oxidant and substrate.

Tropilidene was allowed to react with perbenzoic acid in chloroform at 4°. The solutions contained respectively 1-, 2-, and 3-molar amounts of the reagent, the reactions being followed by titration with potassium iodide and sodium thiosulphate. In the first case, complete absorption of the oxidizing agent was quite rapid, and the main product was a liquid ester, containing at least one benzoate group and probably at least one other oxygen atom. No really satisfactory analysis was obtained, however, and the homogeneity of this product was in doubt. Benzoic acid was also isolated, and since this could hardly have survived the working-up procedure, which employed prolonged stirring with powdered calcium hydroxide, it most probably arose by the pyrolysis of a benzoate derivative during distillation.

In the second and third cases, the amount of perbenzoic acid consumed reached a limiting value of 1.7 moles.

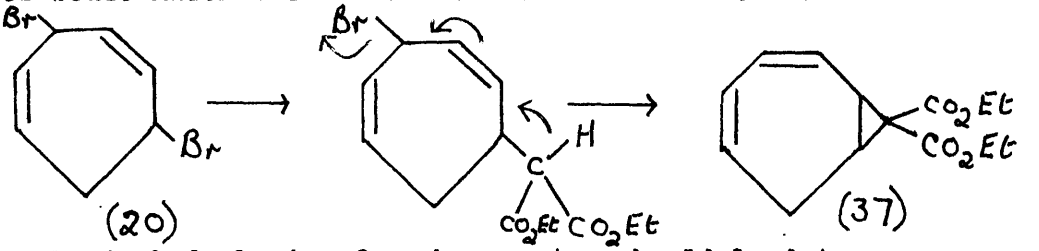
From both products, considerable quantities of a white, crystalline material were obtained. This solid was identified by means of its melting-point, spectral properties, and alkaline hydrolysis to benzoic acid, as being benzoyl peroxide. The liquid products of these two reactions were identical and similar to that obtained using 1 mole of the reagent. Benzoyl peroxide arises from the calcium hydroxide catalyzed condensation of benzoic acid with excess perbenzoic acid at the working-up stage.

On repeating the experiment with excess perbenzoic acid in ethereal solution, a limiting uptake of 1.5 moles was observed. Acidified ferrous ammonium sulphate was employed to remove any benzoyl peroxide formed as described previously, but this treatment must also have decomposed the products of the reaction, as only negligible amounts of material were obtained on evaporation of the ethereal solution.

When tropilidene was treated with performic acid at 50°, and the reaction mixture was steam-distilled, only starting-material and benzaldehyde, isolated and identified as its 2:4-dinitrophenylhydrazone, were recovered.

As previously mentioned in the historical section, the reaction of tropilidene with bromine[5,7] was among the first of its reactions to be studied. The liquid dibromide so obtained, on heating under vacuum, is converted into tropylium bromide[5], and so we have made no attempt to distil it. Treatment of the crude dibromide with

sodium iodide in acetone very rapidly led to the recovery of tropilidene, identified by its very characteristic infra-red spectrum. Furthermore, the dibromide, when treated with sodio-malonic ester, gave a liquid product which did not analyze for the expected cyclopropane derivative (37), arising from an S_N2' reaction of sodio-malonic ester on non-vicinal bromine atoms[57]:-



Basic hydrolysis of such an ester should lead to the cyclopropylcarboxylic acid (38), whereas the ester derived by a straightforward double S_N2 reaction of sodio-malonic ester on the 1,2-dibromide (39) might well cyclize to the keto-ester (40), which would then hydrolyze to the cyclopentanone derivative (41). We have found that the product of hydrolysis is in fact non-acidic. Such evidence as we have is thus in favour of a 1,2-addition mechanism for the formation of the liquid dibromide.

Tropilidene was found to absorb a second molecule of bromine rather more slowly. The tetrabromo-compound is an extremely viscous yellow gum, which is quite unstable under vacuum, and which evolves hydrogen bromide spontaneously.

In an attempt to study the addition of hypobromous acid, tropilidene was treated with moist N-bromosuccinimide in the presence of various acidic catalysts[58]. Only starting-

material and small amounts of benzaldehyde were recovered.

Tropilidene was shaken with a 3-molar excess of N-bromosuccinimide in ethanol[59]. After a few hours, the succinimide formed was filtered off, and the product isolated as a viscous red gum. This material contained at least one bromine atom, but the infra-red spectrum was rather indeterminate, and the compound was unstable under vacuum. The ultra-violet absorption spectrum revealed no maximum above 220 mμ. When only 1 mole of N-bromosuccinimide was used, a yellow oil was obtained, in which the presence of benzaldehyde was established. The proportion of benzaldehyde present, as estimated from the ultra-violet absorption, was around 20%. The product did contain bromine, while there were also indications of -OEt bands in the infra-red, but attempts to obtain the product free from benzaldehyde, by fractional distillation led to extensive decomposition.

It has been known for a long time[3,4] that tropilidene reacts smoothly with 1 mole of hydrogen bromide in acetic acid, to produce an adduct which, like other bromine-containing derivatives in this series, is incapable of being distilled. We isolated this product by careful evaporation at 20°, and allowed it to react with a solution of diethylamine in benzene. The amine so obtained was a colourless, volatile liquid, which afforded a crystalline picrate, and was highly susceptible to aerial oxidation. Its ultra-violet spectrum indicates that either of the formulae, (42) or (43), is the correct one.

The diethylamino-derivative was quite stable towards boiling alkali, while it afforded no solid derivative with 2:4-dinitrophenylhydrazine. The amine appeared to form an adduct with maleic anhydride, but this material was not sufficiently stable to permit isolation. Catalytic hydrogenation resulted in the rapid absorption of 2 moles of hydrogen, there being no indication of the presence of a cyclopropane ring arising from a norcaradiene (9) ($X=H_2$) derivative.

The hydrogen bromide adduct already described was refluxed with potassium acetate in acetic acid. The liquid acetate so obtained was shown by vapour-phase chromatography to be a 3:2-mixture, although a satisfactory analysis was obtained for a diacetate, such as would be obtained by simultaneous metathesis of the hydrogen bromide adduct and addition of acetic acid to give a product like (45). The ultra-violet spectrum indicated that at least one of the components was a conjugated diene. Catalytic hydrogenation over palladium-charcoal confirmed this view, and so it would appear that we are dealing with a mixture of a diene monoacetate such as (44), and an unsaturated diacetate such as (45).

In an attempt to isolate the parent alcohols, the acetate mixture was fully hydrogenated, and the mixture of saturated acetates subjected to lithium aluminium hydride reduction. Two hydroxy-compounds were obtained, the more volatile compound yielding cycloheptanone, identified (melting-point, mixture melting-point, and infra-red), as its 2:4-dinitrophenylhydrazone, on oxidation with

chromium trioxide in acetone. The higher-boiling alcohol, which was presumably a dihydroxy-compound, was obtained in very poor yield on account of its high water-solubility, and so a further attempt to establish the structure of the diacetate component of the mixture was made. Solvolysis of the mixture of unsaturated acetates using sodium in methanol, and manganese dioxide oxidation of the products, yielded a single 2:4-dinitrophenylhydrazone derivative, the structure of which was established, from spectral and analytical data, as the bis-derivative of cyclohept-2-en-1,3-dione (46).

As a result of the two sets of degradative experiments, it is possible to write (44) and (45) as the structures of the original acetates.

By analogy, and in view of the close similarity between the ultra-violet spectra of (44) and (43), the latter may be regarded as the structure of the diethyl-amino-derivative. Accordingly, it seems most likely that hydrogen bromide addition to tropilidene takes place by the 1,2-mechanism.

Tropilidene was catalytically hydrogenated over palladium-charcoal, and the reaction was stopped after only 1 mole of hydrogen had been absorbed. There was no significant decrease in the rate of absorption at this point. Ultra-violet spectral analysis indicated that the mixture of products contained only 9% of conjugated cycloheptadiene, and no unreacted cycloheptatriene. On repeating the hydrogenation over palladium-barium sulphate and stopping it at the same stage, there was again no sign of

a change in the rate of absorption, although the overall rate had suffered a seven-fold decrease. Ultra-violet spectral analysis again indicated the presence of around 10% of conjugated cycloheptadiene among the products. The conclusion to be drawn from this experiment is that the addition of hydrogen is not step-wise, i.e., it does not proceed by 1,2-addition, but is rather conjugate in nature.

Tropilidene wastreated with 1-chloro-1-nitrosocyclohexane (47), prepared by the chlorination of cyclohexanone oxime,[60] in an attempted Diels-Alder type of reaction.[61] The bulk of the tropilidene (65%) was recovered, and there was no evidence for an adduct such as (48).

Unlike benzo-cyclooctatriene (49)[62,63] tropilidene does not appear to form a crystalline complex with ethanolic silver-nitrate solution.

EXPERIMENTAL

Tropilidene - The tropilidene used in this investigation was supplied by the Royal Dutch Shell Company, and was prepared by the thermal isomerization of bicyclo(2:2:1)hepta-2,5-diene. This material had b.p. 115-116°/736 mm., n_D^{22} 1.5182 νmax. 3070 s, 3010 m, 2920 m, 2890 m, 1625 w, 1440 m, 1400 m, 795 vs, 730 vs cm.$^{-1}$ λmax. 262.5 mμ (log ε, 3.48). Vapour-phase chromatography indicated complete homogeneity. The hydrocarbon is very volatile, and was stored at 5° under nitrogen to minimize resinification.

Oxidation of tropilidene with selenium dioxide - (a) Tropilidene (8.80 g., 0.10 m.) was dissolved in acetic anhydride (20 ml.), and treated with a solution of selenium dioxide (5.6 g., 0.05 m.) in water (10 ml.). ~~The~~ The reaction mixture was stirred at 25° for 24 hours, before filtering through a pad of charcoal/Celite and distilling. Only starting-material was recovered.

(b) Using the same molar proportions in a mixture of acetic acid (17 ml.) and acetic anhydride (8 ml.), the reaction mixture was refluxed with stirring for 6 hours. Much more selenium was formed in this case, and this was removed firstly by filtration through charcoal, and then by very rapid (flash) distillation. The bulk of the crude product had b.p. 60-64°/0.4 mm., but was too severely contaminated with selenium and selenium hydride to permit its characterization.

(c) Tropilidene (5.0 g., 0.055 m.) was dissolved in 95% ethanol (50 ml.) and added to a solution of selenium dioxide

(6.1 g., 0.055 m.) in ethanol (55 ml.). The mixture was refluxed with vigorous stirring for 7 hours. After cooling and filtration, the reaction mixture was poured into a large volume of water, carefully neutralized with sodium hydrogen carbonate solution and extracted with chloroform. Filtration of the combined extracts through charcoal gave on evaporation and distillation, two fractions of b.p. 60-70 /12 mm. and 112-114 /12 mm. respectively. The more volatile fraction yielded a 2:4-dinitrophenylhydrazone, m.p. 168°, undepressed on admixture with acetaldehyde 2:4-dinitrophenylhydrazone, indicating that this compound was paraldehyde, formed by oxidation of the solvent. The higher-boiling fraction (300 mg.) had n_D^{21} 1.5730 λmax. (H_2O) 226, 231, 239 s, 312 mμ . No solid derivative was isolated on treatment of this material with solutions of styphnic acid or picric acid. Repetition of the above procedure in 10% aqueous dioxan at 100° for 4 hours afforded a product which was quite hopelessly contaminated with colloidal selenium, and did not reveal any trace of the characteristic ultra-violet absorption of tropone.

Oxidation of tropilidene with manganese dioxide - (a) In this experiment, the manganese dioxide was obtained by heating manganese carbonate at 220° for 42 hours in a current of air, and was not further activated. This grade of manganese dioxide is usually referred to as "MnO_2A". Tropilidene (2.2 g.) was shaken for 24 hours at 20° with MnO_2A (30 g.). Filtration and evaporation gave mostly starting material and a little ketonic material. This

latter compound afforded a 2:4-dinitrophenylhydrazone, m.p. 238°, pale orange needles from acetic acid, undepressed on admixture with an authentic sample of benzaldehyde 2:4-dinitrophenylhydrazone. Infra-red comparison also showed that our "ketonic material" was, in fact, benzaldehyde. (b) MnO_2A was washed with 15% nitric acid, and repeatedly washed with distilled water to pH 4.5. Drying at 200° for 48 hours and powdering, gave the reagent known as "MnO_2B". Treatment of tropilidene with MnO_2B under exactly similar conditions to those already described gave benzaldehyde in 48% yield.

Oxidation of tropilidene with mercuric acetate - Tropilidene (5.0 g., 0.055 m.) was added rapidly to a stirred suspension of mercuric acetate (18.0 g., .057 m.) in acetic acid (80 ml.). The mixture was stirred for 1½ hours at 20°, then refluxed under nitrogen for 2 hours. Upon heating, the solution became dark green and mercury was deposited from solution. The cooled solution was evaporated to small bulk, poured into a large volume of brine and extracted with ether. The usual processing gave on distillation three fractions:-

(i) b.p. 70-76°/12 mm., n_D^{19} 1.5120. λmax. 248,263 mμ.

(ii) b.p. 100-120 /12 mm., n_D^{19} 1.5073. λmax. 243 mμ.

(iii) b.p. 130-140°/12 mm., n_D^{19} 1.4980. λmax. 243 mμ.

Fraction (i) was shown from its infra-red and ultra-violet spectra to consist largely of starting-material, while fraction (ii) also contained considerable quantities of tropilidene. Fraction (iii), however, reveals strong bands in the infra-red at 1740 cm.$^{-1}$, and has λmax. 243 mμ (log , 3.93) based on a molecular weight of 210,

formula (36). It did not, however, form a Diels-Alder adduct with maleic anhydride in xylene. All three fractions gave orange colours in alcohol, on adding concd. sulphuric acid.

The experiment was repeated under identical conditions, using 2 moles of mercuric acetate. Distillation gave two definite fractions (i) b.p. 64-68°/1.6 mm., n_D^{20} 1.5082 (1.0 g.), and (ii) b.p. 104-109°/1.6 mm., n_D^{20} 1.4918 (2.7 g.), together with an intermediate cut (1.0 g.). Both fractions gave precipitates with 2:4-dinitrophenylhydrazine reagent, but these solids were non-crystalline, and were shown by ultra-violet spectroscopy to consist of complex mixtures of derivatives. The presence of mercury in these fractions, and in those from the preceding experiment, was shown by heating with cupric oxide and allowing the vapours to come in contact with a spot of palladous chloride on filter paper. A dark stain was produced in each case.

Oxidation of tropilidene with lead tetraäcetate - Tropilidene (2.64 g., 0.029 m.) was refluxed in dry benzene (25 ml.), containing lead tetraäcetate (12.72 g., 0.029 m.), for 20 hours, with stirring. At the end of this time, moist starch-potassium iodide test paper was not affected by a drop of the reaction mixture, and the lead acetate collected by filtration corresponded to 100% reduction of the oxidant. The filtrate was washed (sodium hydrogen carbonate, water), dried (magnesium sulphate), and evaporated. Distillation gave only one material (2.2 g.), b.p. 75-90°/0.2 mm. νmax. 1760-1740, 1250 $cm.^{-1}$

λmax. 248 mμ (log ε, 3.4).

The infra-red spectrum of the above product indicated that a mixture of acetates was probably present. The mixture was dissolved in methanol containing a small amount of sodium methoxide, and allowed to remain at 20° for 18 hours. Addition of water, and saturation of the resulting solution with carbon dioxide, gave on extraction with ether and evaporation, a crude hydroxylic material. This mixture was unaffected by active manganese dioxide in a 1:1-mixture of petrol and chloroform after 20 hours shaking.

Oxidation of tropilidene with tert-butyl perbenzoate -

Tropilidene (4.05 g., 0.044 m.) was allowed to react with cuprous bromide (50 mg.) and tert-butyl perbenzoate (3.5 g., 0.018 m.) at 100-110° under nitrogen for 2 hours, in the absence of solvent. The dark-coloured mixture was then cooled, extracted with ether, washed (2N sodium carbonate, water), dried and evaporated. Distillation gave two main fractions:-

(i) b.p. 66-80°/0.2 mm., n_D^{19} 1.5723. Colourless liquid.
(ii) b.p. 80-125°/0.2 mm. Yellow, semi-solid.

The first of these was redistilled, b.p. 78-80°/0.14 mm., n_D^{19} 1.5709. $\lambda_1$max. 226 mμ (log ε, 4.32). λ_2 max. 301 mμ (log ε, 3.70). (Found: C, 64.73; H, 5.73). The second fraction was acidic, and was separated by carbonate extraction into a solid acid, m.p. 122°, and a neutral fraction. The acid was shown (m.p., mixture m.p., and infra-red) to be benzoic acid. The neutral liquid was redistilled, b.p. 130°/0.3 mm., n_D^{18} 1.5489. λmax. 231 mμ

($\log \varepsilon$, 4.07). (Found: C, 77.29; H, 6.95. $C_{14}H_{12}O_2$ (monobenzoate) requires C, 79.22; H, 5.70%).

Oxidation of tropilidene with sodium dichromate - Tropilidene (5.0 g., 0.055 m.) and sodium dichromate (26.0 g.) were heated in acetic acid solution (100 ml.) at 95-100°. A vigorous exothermic reaction soon set in, and then the mixture was cooled, diluted with a large volume of water and extracted with petrol (b.p. 40-60°). The aqueous acetic acid solution was then distilled under reduced pressure to small volume, before extraction with ether in the usual way. The petrol extract contained a mixture (1.6 g.) of benzaldehyde and tropilidene, while the ether extract was found to contain a mixture (2.4 g.) of benzaldehyde and benzoic acid.

Attempted nitrosation of tropilidene - To a mixture of tropilidene (5.0 g., 0.055 m.) and iso-amyl nitrite, (6.5 g., 0.055 m.) was added a cooled solution of sodium (1.27 g., 0.055 m.) in ethanol (45 ml.) over a period of 45 mins. at 0-5°, with stirring. When the addition was complete, the mixture was allowed to stand for 24 hours at 4°, before evaporating to small volume at 20°, diluting with water, and extracting with ether. The residual aqueous solution was then acidified with dilute hydrochloric acid to pH 4-5, and re-extracted. This ether extract afforded after the usual processing a dark red oil (0.7 g.), from which no solid oxime was obtained after chromatography on Grade III (neutral) alumina. From the original ether extract, tropilidene (3.2 g.) was recovered unchanged.

Attempted epoxidation of tropilidene - (a) Tropilidene (1.76 g., 0.019 m.) was allowed to stand for 72 hours in an ethereal solution of monoperphthalic acid (3.84 g., .021 m.) at 20°. The phthalic acid produced was then filtered off, and the ethereal solution washed (sodium hydrogen carbonate, water,) dried, and evaporated. Only tropilidene (1.2 g.) was obtained by this means. Acidification and prolonged ether-extraction of the sodium hydrogen carbonate washings yielded no further product. Repetition of the experiment with two, and then five, moles of the oxidant led to the same result.

(b) Samples of tropilidene (1.39 g., 0.015 m.) in three flasks were allowed to react with solutions of perbenzoic acid in chloroform containing 2.07 g., 4.14 g., and 6.21 g. respectively, i.e. in 1-, 2-, and 3-molar amounts. The reactions were carried out at around 4°, and were followed by the titration of aliquots against potassium iodide/ sodium thiosulphate in the usual way. The results, all of which are corrected for self-decomposition of the oxidant are contained in the following table:-

No. of moles of perbenzoic acid	% age reagent left after 24 hrs.	% age reagent left after 48 hrs.	% age reagent left after 116 hrs.
1	0	-	-
2	15.7	12.0	-
3	45.1	41.6	39.2

The products in each case were isolated by stirring the solution with powdered calcium hydroxide until neutral, filtration and evaporation.

(i) From the experiment carried out with 1 mole of perbenzoic acid, distillation afforded two fractions. The first was a colourless liquid b.p. 70-80°/0.02 mm., n_D^{25} 1.5202 ν max. 3450, 1735 cm.$^{-1}$ λ max. 227 mμ (log ε, 3.88) (Found: C, 62.07; H, 5.86. $C_{14}H_{14}O_5$ requires C,64.12; H, 5.34%). The second fraction rapidly solidified and had m.p. 122° on recrystallization from water, undepressed on admixture with authentic benzoic acid.

(ii) From the experiment with 2 and 3 moles of perbenzoic acid the products were essentially the same. Each consisted of a dark red gum from which a beautiful white crystalline compound was obtained on trituration with methanol. The yield of this compound was 150 mg. from the reaction with 2 moles of perbenzoic acid, and 350 mg. from the other. The solid had m.p. 108°, white needles from ethanol. $\nu_{max.}^{CCl_4}$ 1785 m., 1770s. cm.$^{-1}$ λmax. 236 mμ (logε, 4.46) (Found: C, 69.49; H, 4.67: $C_{14}H_{10}O_4$ requires C, 69.42: H, 4.16%). Hydrolysis of the solid (120 mg.) with 2N sodium hydroxide yielded on acidification benzoic acid (103 mg.). The evidence obtained indicates that this "product" is in fact benzoyl peroxide. After removal of the peroxide, distillation afforded from each of the crude products a liquid ester identical with that obtained in experiment (i).

Repetition of this experiment with 2 moles of perbenzoic acid in ethereal solution led to an essentially similar result, 1.5 moles of the reagent being absorbed after 120 hours. After treatment with calcium hydroxide in the usual way, the ethereal solution was then shaken with saturated ferrous ammonium sulphate solution, acidified with sulphuric

acid, to remove any benzoyl peroxide present. This procedure must also have caused the decomposition of any epoxides present, as on evaporation of the ethereal solution negligible amounts of product were obtained.

(c) Tropilidene (2.0 g.) was added to a mixture of 98% formic acid (23 ml.) and 30% hydrogen peroxide (4 ml.). The temperature was allowed to rise spontaneously to 50°, and maintained at 50-55° for 4 hours. (Homogeneity of the solution is only attained at temperatures over 50°). The mixture was cooled, poured into water, and steam-distilled. Ether extraction of the steam-volatile material afforded only tropilidene and a small amount of benzaldehyde, isolated and identified as its 2:4-dinitrophenylhydrazone. The residue from the steam-distillation was basified with 4N sodium hydroxide, warmed at 100° for 30 mins., and poured on to ice and dilute hydrochloric acid. Constant ether-extraction afforded no further product.

Addition of bromine to tropilidene - (a) Tropilidene (2.76 g., 0.03 m.) was dissolved in dry carbon tetrachloride (30 ml.) at 0°, before adding bromine (5.4 g., 0.03 m.) in carbon tetrachloride (20 ml.) over a period of 20 mins., with stirring. Removal of the solvent under reduced pressure at 20° afforded a viscous, pale yellow oil. This material darkened rapidly under vacuum, even at 20°, and no attempt was made to distil it. The crude product had n_D^{18} 1.6171. $\lambda_{max.}$ 271 mμ (log ε, 3.62).

(b) Tropilidene (2.76 g., 0.03 m.) was dissolved in dry

carbon tetrachloride (40 ml.) at 0°, and bromine (10.8 g., 0.06 m.) in carbon tetrachloride (40 ml.) was added slowly, with stirring. After 1 mole of bromine had been absorbed the reaction became much slower, the total time for the addition being 5 hours. The product was isolated as in the previous experiment as an extremely viscous yellow oil, which was quite unstable under vacuum, and evolved hydrogen bromide on standing. Attempts to obtain crystalline material from the gum were unsuccessful.

Reaction of liquid dibromide with sodium iodide - The dibromide (3.14 g., 0.018 m.) was dissolved in dry acetone (15 ml.) and sodium iodide (15.0 g., 0.1m.) in acetone was added quite rapidly. Iodine was liberated at once, and after 15 mins. the solution was evaporated carefully at 20° to half its volume, poured into brine, and extracted with ether. Washing (sodium thiosulphate, brine), drying, and evaporation of the ether extracts afforded tropilidene (1.3 g.), identified by its very characteristic infra-red spectrum.

Reaction of liquid dibromide with sodio-malonic ester - Sodio-malonic ester was prepared from redistilled diethyl malonate (10.7 g., 0.067 m.) and sodium (1.5 g., 0.065 m.) in ethanol (20 ml.). The dibromide (8.4 g., 0.033 m.) in ethanol (10 ml.) was added over a period of 15 mins. at 20°. The reaction mixture was stirred for 16 hours at this temperature, and then refluxed for 2 hours. Most of the ethanol was then removed under reduced pressure, and the product isolated by pouring the residue into water, and extracting with ether. Distillation afforded diethyl malonate (4.8 g., 45%), b.p. 54-56°/0.35 mm., n_D^{25} 1.4170; and a higher boiling product b.p. 120-125°/0.35 mm., n_D^{25} 1.4911 $\lambda_{max.}$ 250 mμ

(log ε ,3.24) ν_{max} 1720, 1610 cm.$^{-1}$ (Found: C, 64.86; H, 7.66. $C_{16}H_{20}O_5$ (40) requires C,65.65: H, 6.85%).

Hydrolysis of this product with 50% aqueous potassium hydroxide at 20°, extraction with ether, and acidification and re-extraction with ether, afforded negligible amounts of material from the second ether extract, indicating that no acid such as (38) was formed. The ether extract from the alkaline solution yielded only a complex mixture of products.

Attempted addition of HOBr to tropilidene - Tropilidene (2.0 g., 0.022m.) was shaken with N-bromosuccinimide (3.5 g.,0.020 m.) in a mixture of dioxan (5 ml.) and water (2.5 ml.), containing 10 drops of glacial acetic acid, at 20° for 16 hours. The reaction mixture was then extracted with ether. The ethereal extracts were washed (sodium bisulphite, sodium hydrogen carbonate, water), dried (magnesium sulphate), and evaporated. Tropilidene, identified by its infra-red spectrum, was the only compound present. Repetition of the experiment using a trace of concd. sulphuric acid as catalyst led to essentially the same result, although small amounts of benzaldehyde, isolated and identified as its 2:4-dinitrophenylhydrazone, were formed.

Reaction of tropilidene with EtOBr - (a) Tropilidene (2.68 g., 0.029 m.) was shaken at 20° in ethanol (90 ml.) containing recrystallized N-bromosuccinimide (16.6 g., 0.09 m.). After 20 hours, the reaction mixture was chilled, filtered to remove succinimide, and evaporated at 20° to small volume

before pouring into a large volume of water. Ether extraction followed by the usual processing afforded a viscous red gum, which was quite unstable under vacuum, and could not be distilled. λ max. 235 mμ (log ε, 3.19). The infra-red spectrum was ill-defined, but elemental analysis confirmed the presence of bromine indicated by its instability under vacuum.

(b) The reaction was repeated under identical conditions, but using only 1 mole of N-bromosuccinimide. The crude product was a yellow oil. A sample of this oil afforded the 2:4-dinitrophenylhydrazone of benzaldehyde, m.p. 238°, on treatment with a methanolic, hydrochloric acid solution of the reagent at 20°. The ultra-violet spectrum (λmax. 245 mμ) indicated the presence of about 20% of benzaldehyde. Attempted fractional distillation of the product led to extensive blackening - only small amounts of distillate being collected. All three cuts collected contained bromine and exhibited an intense infra-red absorption band at 1100 cm.$^{-1}$, thus indicating that some of the expected adduct was present, but the presence of benzaldehyde precluded the use of any quantitative spectral or analytical measurements.

Addition of HBr to tropilidene - A 40% solution of hydrogen bromide (18 g., 0.22 m.) in glacial acetic acid was added to tropilidene (20 g., 0.22 m.) at 0°, over a period of 15 mins. The reaction mixture was then allowed to warm up to 20°, and was shaken for a further 15 mins., before cooling and adding crushed ice (200 g.). The heavy oil which separated was extracted with petrol (b.p. 60-80°), washed

repeatedly with ice-water, and dried (calcium chloride). Evaporation afforded a reddish, viscous oil which was not distilled.

Preparation of 6-diethylamino-cyclohepta-1,3-diene (43) - The crude hydrogen bromide adduct was dissolved in dry benzene (50 ml.) and treated with excess diethylamine in benzene solution. After 16 hours at 20°, the semi-solid mass was washed with 6N hydrochloric acid. The free amine was then regenerated from the acidic extract with solid potassium hydroxide, extracted with ether, washed (water), and dried (sodium sulphate). Distillation afforded the amine as a colourless liquid b.p. 48°/0.07 mm. n_D^{20} 1.4934. (The overall yield from tropilidene was 33%) λmax. 246 mμ (log ε,3.59). The amine was susceptible to aerial oxidation, and was stored under nitrogen at 0°.

The 6-diethylamino-cyclohepta-1,3-diene formed a picrate on warming at 100° for 10 mins. with a saturated ethanolic solution of the reagent. Recrystallization from ethanol afforded yellow leaflets, m.p. 126° (Found: C, 52.02; H, 5.09; N, 14.29. $C_{17}H_{22}N_4O_7$ requires C,51.77; H, 5.62; N,14.21%).

The unsaturated diethylamino-derivative was hydrogenated over 10% palladium-charcoal. The absorption of hydrogen was equivalent to 2.05 double bonds. This saturated amine also formed a picrate, m.p. 85° (ethanol). (Found: C,51.44; H,6.24; N,13.99. $C_{17}H_{26}N_4O_7$ requires C,51.25; H, 6.58; N, 14.06%).

6-Diethylamino-cyclohepta-1,3-diene was recovered unchanged from 2N sulphuric acid after 24 hours, under nitrogen.

Treatment of the amine with a hot methanolic, hydrochloric acid solution of 2:4-dinitrophenylhydrazine gave no solid derivative.

The amine was unaffected by refluxing in 10% alcoholic potassium hydroxide solution.

6-Diethylamino-cyclohepta-1,3-diene appeared to form a Diels-Alder adduct with maleic anhydride in refluxing benzene solution, but this material decomposed when any attempt was made to isolate it.

Preparation of 6-acetoxy-cyclohepta-1,3-diene (44) - The crude hydrogen bromide adduct (20 g.) already described was refluxed for 2 hours under nitrogen, with a solution of potassium acetate (25 g.) in glacial acetic acid (100 ml.). After cooling and filtration of the solution to remove potassium bromide (11.9 g.), the filtrate was evaporated to half its volume under reduced pressure, and poured into a large volume of ice-water. The usual processing gave on distillation a product of b.p. 56-60°/0.2 mm., n_D^{23} 1.4931. νmax. 1735, 1240 cm.$^{-1}$ λmax. 243 mμ (log. ε, 3.55). (Found: C, 62.29; H, 7.35. $C_{11}H_{16}O_4$ (diacetate) requires C,62.25; H, 7.60%). Examination of this product by vapour-phase chromatography, revealed that it was in fact a 3:2-mixture of compounds.

Catalytic hydrogenation of the mixture over 5% palladium-charcoal in ethyl acetate, led to the uptake of 2.11 moles of hydrogen, assessed on the basis of M.W. 212 (diacetate). The saturated acetate so obtained was distilled b.p. 50°/0.1 mm., n_D^{21} 1.4554 (Found: C, 65.54; H, 9.78. $C_{11}H_{18}O_4$ (diacetate) requires C, 61.66; H, 8.47%. $C_9H_{16}O_2$

(monoacetate) requires C, 69.19; H,10.32%).

The saturated acetate mixture (1.08 g.) was dissolved in dry ether (10 ml.) and added over a period of 3 mins. to a slurry of lithium aluminium hydride (0.38 g.) in ether (25 ml.). After stirring for 30 mins. at 20°, and refluxing for a further 30 mins., the excess hydride was decomposed with an ethereal solution of ethyl acetate. The mixture was then poured into ice-cold 2N sulphuric acid and worked-up in the usual way. Distillation yielded two fractions, b.p. 60°/0.2 mm. n_D^{24} 1.4761, and b.p. 110-120°/0.2 mm., n_D^{24} 1.4964. The total yield obtained was very poor, due in part to the high water-solubility of the expected alcohols.

The lower-boiling fraction was dissolved in 'Analar' acetone (1 ml.) and titrated with 8N chromic acid at 20°. The reaction mixture was poured into water, and extraction with ether afforded a carbonyl compound. This ketone gave a yellow 2:4-dinitrophenylhydrazone, m.p. 147° (ethanol). Melting-point on admixture with the 2:4-dinitrophenylhydrazone of cycloheptanone 145-148°. λmax. ($CHCl_3$) 366 mμ (log ε, 4.37) (Found: C,53.69; H,5.16; N,19.30. $C_{13}H_{16}N_4O_4$ requires C, 53.42; H, 5.52; N, 19.17%)

The higher-boiling fraction was almost certainly a diol, but there was insufficient material to investigate.

The mixture of unsaturated acetates (5.83 g.)was dissolved in dry methanol (40 ml.), containing a little dissolved sodium (200 mg.). After 24 hours at 20°, a little water was added, and the solution saturated with carbon dioxide, filtered, evaporated and distilled:-

(i) b.p. 94-110°/0.2 mm. n_D^{24} 1.5211.
(ii) b.p. 110-130°/0.2 mm. n_D^{24} 1.5213.
(iii) b.p. 130-150°/0.2 mm. n_D^{24} 1.5210.

Obviously, the product so obtained is a mixture of alcohols. Accordingly, the three cuts were re-combined and a sample (700 mg.) shaken with active manganese dioxide (15.0 g.) in petrol, containing 15% chloroform to dissolve the alcohols. After 96 hours, the infra-red spectrum of the crude product still revealed the presence of hydroxylic material, but there was also a strong band at 1650 $cm.^{-1}$ Treatment of the mixture with excess 2:4-dinitrophenylhydrazine produced a single, crimson derivative, m.p. 315 (dec.) (dioxan). $\lambda_{max.}$ ($CHCl_3$) 412 mμ (log ε, 4.72). (Found: C,47.75; H, 3.17; N,22.97. $C_{19}H_{16}N_8O_8$ requires C, 47.11; H, 3.31; N, 23.14%).

Catalytic hydrogenation of tropilidene - (a) Tropilidene (2.28 g.) was hydrogenated over 10% palladium-charcoal in ethyl acetate. The reaction was stopped after 10 minutes, when 595 cc. of hydrogen, equivalent to 1 mole, had been absorbed, although there was no noticeable change in the rate of absorption at this point. Filtration, and careful fractionation of the ethyl acetate solution at 760 mm. to remove the solvent, led to the isolation of a liquid (1.85 g.), n_D^{26} 1.4023. $\lambda_{max.}$ 251 mμ (log ε ,2.82), equivalent to 9% of cyclohepta-1,3-diene. There was no absorption band at 263 mμ, corresponding to tropilidene itself.

(b) Tropilidene (2.60 g.) was hydrogenated over 1% palladium-barium sulphate. After 70 mins., 695 c.c. of hydrogen, equivalent to 1 mole, had been absorbed. There was again no alteration in the rate of reaction at this point, when the reaction was stopped. The liquid (2.28 g.) obtained as in the previous experiment had n_D^{25} 1.4224. λ max. 251mμ(log ε, 3.00), corresponding to 13% of cyclohepta-1,3-diene. There was no spectral evidence for the presence of unreacted tropilidene.

Attempted formation of a Diels-Alder adduct from tropilidene and 1-chloro-1-nitroso-cyclohexane (47) - 1-chloro-1-nitroso-cyclohexane was prepared by the method of Müller et al.,[60] from the chlorination of cyclohexanone oxime. It is a royal blue liquid with an intensely pungent odour, b.p. 54-56°/20 mm., n_D^{20} 1.4620. Tropilidene (2.5 g., 0.027 m.) was allowed to react with 1-chloro-1-nitroso-cyclohexane (4.0 g., 0.027 m.) in a mixture of benzene (7.5 ml.) and ethanol (1.5 ml.). After 6 days, the solvent was removed at 20°, and the residue dissolved in ether. The ethereal solution, which was a deep blue colour, was washed thoroughly with 6N hydrochloric acid. Evaporation of the ethereal solution led to the recovery of 60% of starting-material. From the hydrochloric acid washings no basic material was recovered on rendering the solution alkaline with solid potassium hydroxide.

Attempted formation of a silver nitrate complex of tropilidene - Tropilidene (500 mg.) in ethanol (5 ml.) was added to a solution of silver nitrate in refluxing ethanol (10 ml.). After refluxing for 2 minutes, the solution was set aside. No crystalline material was obtained on prolonged standing, or on evaporation.

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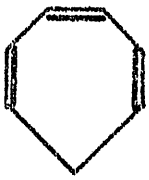

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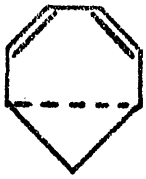

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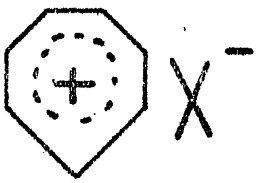

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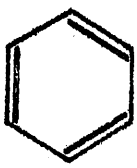

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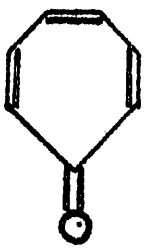

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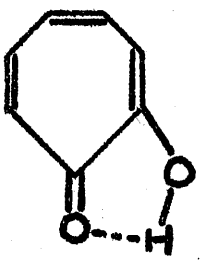

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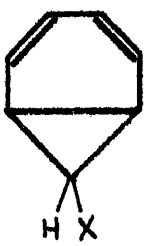

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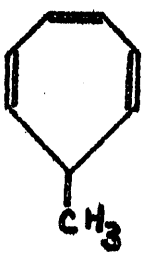

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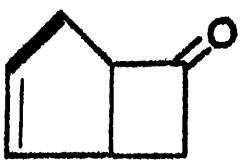

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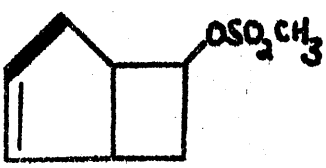

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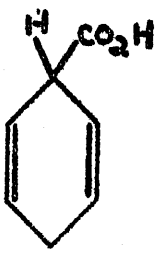

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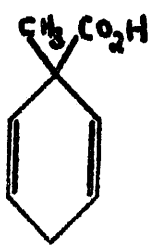

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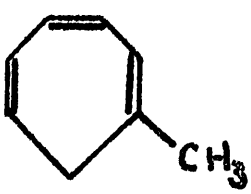

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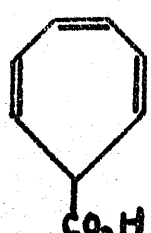

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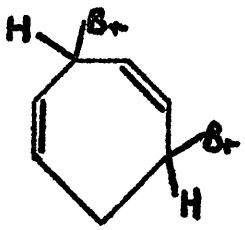

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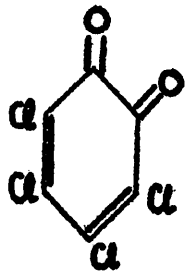

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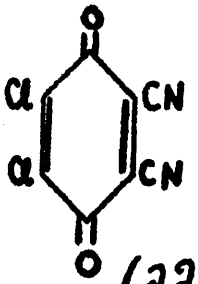

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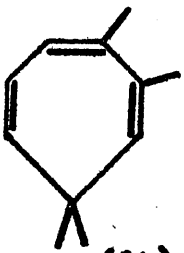

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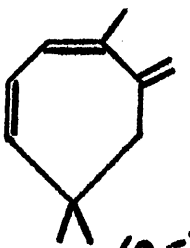

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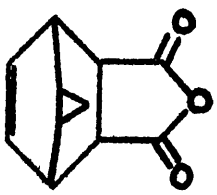

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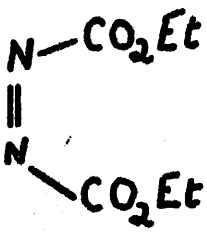

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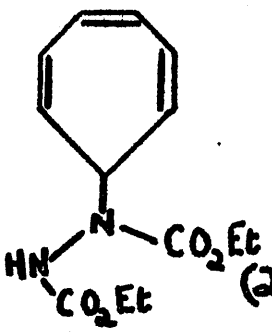

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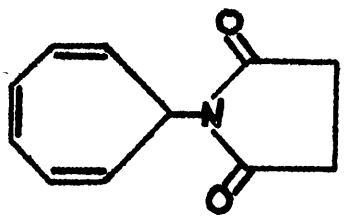

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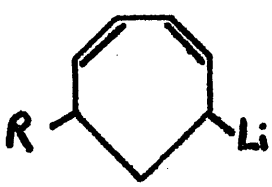

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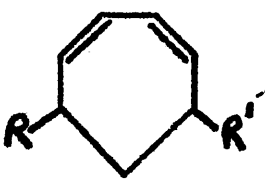

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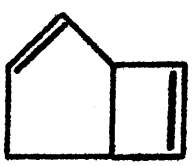

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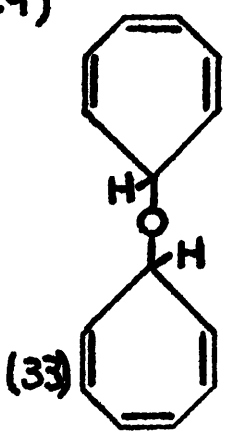

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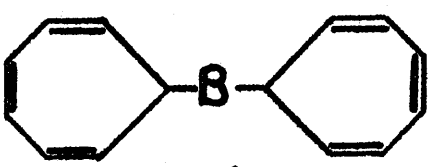

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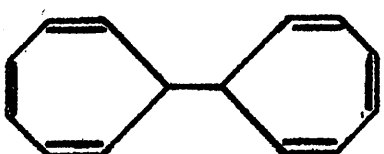

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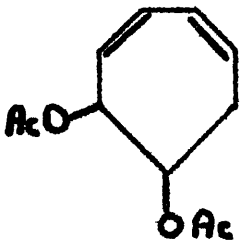

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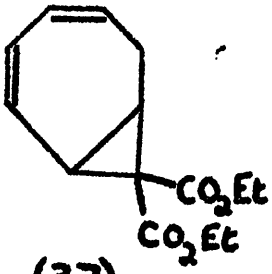

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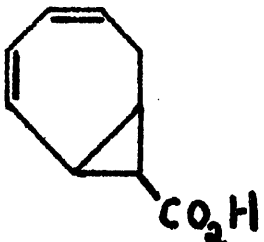

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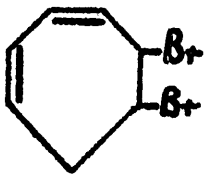

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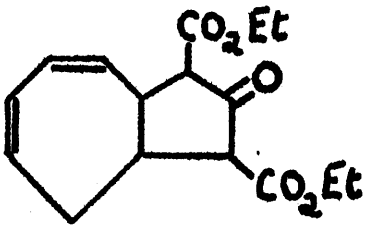

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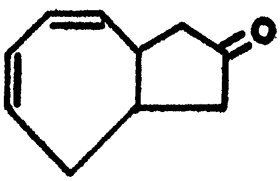

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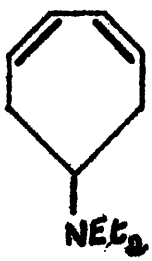

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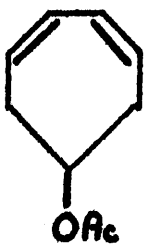

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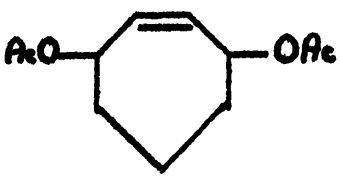

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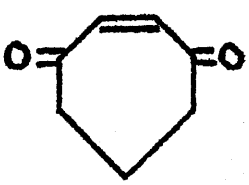

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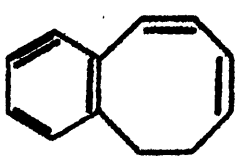

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SECTION II

ELABORATION PRODUCTS OF EUCARVONE

HISTORICAL INTRODUCTION

Eucarvone, a terpenoid trimethylcycloheptadienone (1), was first prepared by Baeyer[1], in 1894 from the reaction of the hydrobromide (3) of the monoterpenoid ketone carvone (2), with methanolic potassium hydroxide. Eucarvone was classified as a monoterpene by virtue of its derivation, and its isoprenoid skeleton. The first, and indeed as yet the sole, reported occurrence of eucarvone in nature was in 1931, when it was isolated by Kaku and his co-workers[2] from the essential oil of Asarum Sieboldi var. seoulensis Nakai.

The correct structure for eucarvone was not established until some ten years after its original isolation. This was due in part to uncertainties regarding the structure of carvone (2) itself, and in part to the fact that eucarvone was optically inactive, although prepared from dextro-rotatory carvone. Both ketones were converted by acid to the isomeric carvacrol (4).[1,3]

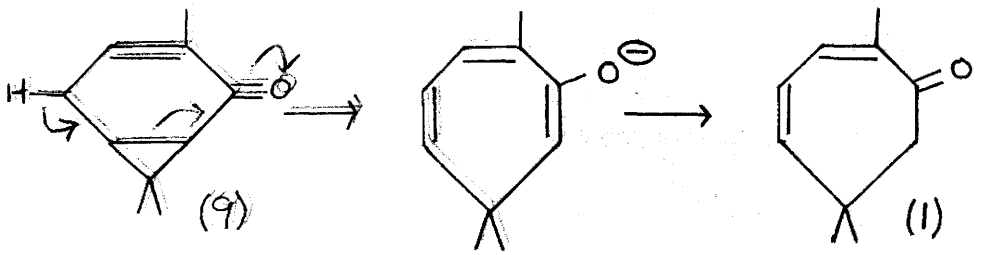
Baeyer[1] made the first contribution to the structural problem by his suggestion that carvone possessed the cross-conjugated cyclohexadienone structure (5), while eucarvone was the conjugated cyclohexadienone (6). However, shortly afterwards the correct structure for carvone [4,5] was established, and Baeyer developed a new concept of the interconversion of carvone and eucarvone. Under the same conditions as those used in the preparation of eucarvone, Baeyer[6] isolated from dihydrocarvone (7) a further ketone carone (8), which, like (7), afforded carveol (10) on

treatment with sulphuric acid. Having established the structure of carone, Baeyer[7] later suggested the analogous carenone formula (9) for eucarvone.

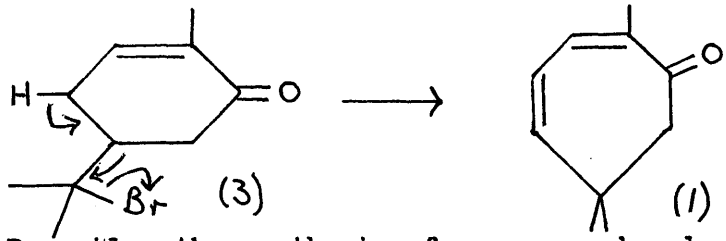
Reduction of eucarvone with sodium in ethanol gave dihydroeucarveol (11), which then afforded the dihydroketone (12) on oxidation with chromium trioxide.[1,6] Baeyer[7] noted that dihydroeucarvone, like eucarvone itself, but unlike carone (8)[8], yielded α,α-dimethylsuccinic acid (14), not cis-caronic acid (13), on permanganate oxidation. At the same time Baeyer showed that tetrahydroeucarvone (15) gave β,β-dimethylpimelic acid (16) on treatment with potassium permanganate, followed by sodium hypobromite. Although this work seemed to establish the presence of a seven-membered ring in eucarvone and its derivatives, Baeyer held to the view that eucarvone actually possessed the carenone structure (9) in which the cyclopropane ring was rendered very labile by the presence of the double bond.

Obvious drawbacks in the bicyclic formulation were the observations that catalytic reduction of eucarvone (1), unlike carone (8), yielded no carvomenthol (17) and that a reversal of the mode of preparation of eucarvone, by treating it with hydrogen chloride, failed to yield any carvone hydrochloride. The question of structure was then considered by Wallach between 1895 and 1905. To explain the above results, and additional ones such as the fact that eucarvone forms a monobenzylidene[9,10] derivative and an unsaturated hydroxylamino-oxime (18)[11], Wallach proposed the now fully authenticated structure (1).[12]

Wallach suggested that the formation of eucarvone from carvone hydrobromide proceeded via the bicyclic carenone structure (9). This compound, he considered, decomposed rapidly in the presence of base to yield the δ-hydroxy-ketone (19), and finally, eucarvone (1) by base-catalyzed dehydration. Clark and Lapworth[13] seemed to furnish evidence in support of this mechanism by virtue of the fact that cyanocarone (20) yielded eucarvone on treatment with a basic solution of ferrous hydroxide. The question remained open until 1957 when a very elegant proof of the mechanism appeared. In this paper, van Tamelen and his collaborators[14] reported the isolation of the intermediate (22) by treating the p-toluenesulphonate of 3-hydroxymethyltetralone (21), with excess base. Indeed, drastic conditions were necessary to obtain the expected cycloheptenone derivative (23). Similarly, the same authors claimed good spectroscopic evidence for the intermediacy of norcarenone (25) in the base-catalyzed conversion of (24) to cycloheptadienone (26). By carefully controlling the pH of the solution, it was apparent from the spectroscopic evidence that carenone (9) was an intermediate in the preparation of eucarvone itself. The second stage of the reaction does not in their opinion, proceed via the intermediate δ-hydroxy-ketone proposed by Wallach, but by an "anion-activation" process, thus:-



The work of van Tamelen and his co-workers also rules out the alternative "synchronous" mechanistic possibility:-



Recently, the synthesis of eucarvone has been reported.[15] Ring-expansion of the readily available 2,2-dimethylcyclohexanone (27) with diazo-methane afforded 3,3-dimethylcycloheptanone (28) as the sole product. Methylation of this ketone in turn yielded exclusively tetrahydroeucarvone (15). Bromination of the saturated ketone followed by dehydrobromination then gave β-dihydroeucarvone (29). Finally, repetition of this procedure afforded a dienone, which was shown to be identical with eucarvone (1).

Much attention has been focussed on the reduction products obtainable from eucarvone. In addition to that dihydro-derivative (12) prepared by the chromium trioxide oxidation of dihydroeucarveol (11), a further dihydro-ketone was obtained by Wallach[16]. Catalytic hydrogenation of eucarvoxime and regeneration of the carbonyl function afforded the compound (29). This structure was assigned largely on the basis of its oxidation to β,β-dimethyladipic acid and from the fact that it did not yield a nitroso-derivative, unlike compound (12). The conjugated dihydro-eucarvone is commonly referred to as β-dihydroeucarvone and its unconjugated isomer

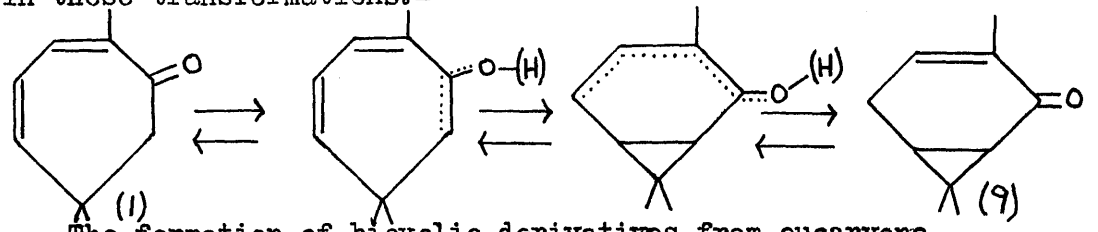
as α-dihydroeucarvone.

Any remaining doubts regarding the structures of eucarvone and the two dihydro-derivatives were largely dispelled by the work of Gillam and West[17] in 1942. These authors measured the ultra-violet absorption spectra of all three ketones and their semicarbazone derivatives, and found them to be in agreement with the accepted structures assigned by Wallach. More recently, β-dihydroeucarvone has been prepared by the catalytic hydrogenation of eucarvone[18]. The final product of this reduction was tetrahydroeucarvone (15), but it proved possible to isolate the dihydro-compound quite readily. Campbell and his collaborators[19] reported the isolation of both dihydro-ketones from the acid treatment of eucarvol (30), which was readily obtained by lithium aluminium hydride reduction of eucarvone. Eucarvane (31), the parent hydrocarbon of the series, was prepared by Ruzicka and Seidel[20] by Wolff-Kishner reduction of tetrahydroeucarvone (15).

In recent years, Corey and his co-workers[21,22] have obtained evidence for the transformation of eucarvone into bicyclic derivatives, especially under basic conditions, and by the use of electrophilic reagents. The structure of the monobenzylidene derivative referred to earlier[9,10] has been established as (32), while the effect of butyl nitrite in base was to produce oximino-eucarvone (33). Treatment of the sodio-salt of eucarvone with methyl iodide gave the methylcarenone derivative (34). Oxidation of eucarvone with selenium dioxide afforded

principally carenolone (35), which was then oxidized by manganese dioxide to carenedione (36).

Corey and his collaborators[23,24] have undertaken an extensive physico-chemical study of some of the above reactions, and, im particular of the constitution of the enolic and the enolate-anion forms of eucarvone. As a result of this study the authors were able to determine the nature of the ring-bridging step involved in these transformations:-



The formation of bicyclic derivatives from eucarvone may occur in one of three distinct ways:-

(a) by way of the anion or enol of the bicyclic isomer (9),

(b) by a fully synchronous process, and

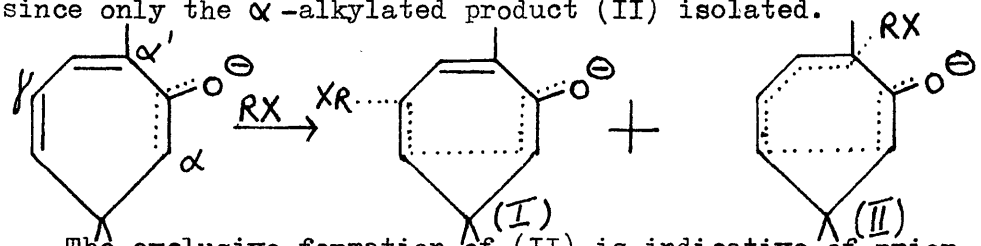
(c) by a mechanism in which substitution precedes bridging.

The third possibility may be excluded by an examination of the product of methylation (34), while it is unlikely that ring-bridging of a dione such as (37) formed by selenium dioxide oxidation would yield only one of the two possible hydroxy-ketones, namely carenolone (35).

To enable a decision between the two remaining possibilities to be reached, Corey[24] showed that, in eucarvone itself, trace amounts of the bicyclic form (9)

must be present, since deuterium-exchange experiments revealed the presence of three replaceable hydrogen atoms. Nuclear magnetic resonance experiments[23] showed, however, that the enolate esters, prepared from sodio-eucarvone possess the monocyclic triene structure (38) exclusively, and are not in thermal equilibrium with their bicyclic tautomers (39). Ultra-violet evidence and the result of very careful neutralization experiments indicated that the enolate anion also existed almost entirely in the monocyclic form.

The authors[24] are of the opinion that the ring-bridging step in a base-catalyzed reaction of eucarvone is not synchronous with nucleophilic attack, i.e., these reactions are not of the transannular S_N2' type. This follows from the constitution of the methylation product (34), since only the α'-alkylated product (II) isolated.



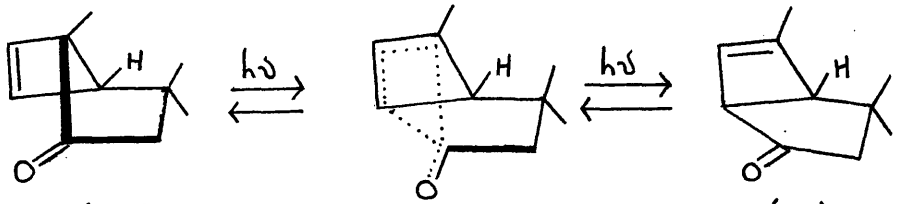
The exclusive formation of (II) is indicative of prior formation of the anion of the bicyclic carenone (9), and α-alkylation of the γ-extended enolate.

With regard to the selenium dioxide reaction mechanism, Corey and his co-workers consider that electrophilic attack upon eucarvone may lead, and indeed induce, the ring-bridging step. Accordingly, at least two

mechanisms are available for the formation of bicyclic derivatives of eucarvone. The role of ring-bridging in these reactions is enhanced, not only by the ease of bridging, but also by the steric effect of the gem-dimethyl grouping, which undoubtedly shields the adjacent α-carbon atom in eucarvone, or its enolate, from straightforward substitution processes.

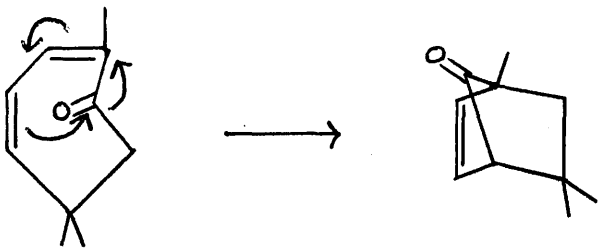
Within the past few months, two groups of workers have studied the photochemical transformations of eucarvone. Büchi and Burgess[25] have isolated two isomeric ketones (40) and (41), by irradiating eucarvone in ethanol, while Hurst and Whitham[26] claim to have isolated an additional isomer (42) of the norbornane type by conducting the irradiation in aqueous acetic acid.

The formation of the valence tautomer (40) has several analogies, but the further rearrangement of this compound to (41) is rather unusual. Büchi and Burgess have suggested that this second rearrangement is unlikely to proceed by a 1,3-methyl migration, but rather by means of a cyclobutane-type transition state as shown:-



(40) (41)

Hurst and Whitham consider that the novel formation of 1,5,5-trimethylnorborn-2-en-7-one (42) occurs by the collapse of an excited state of eucarvone as shown:-



(1) (42)

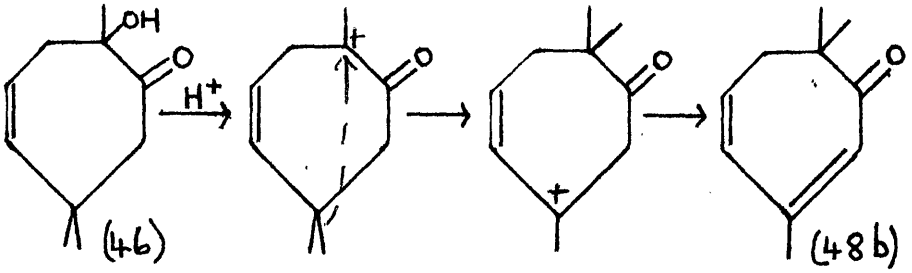
DISCUSSION

In an attempt to prepare the interesting α-diketone (43), in which the gem-dimethyl group blocks enolization to the tropolone structure (44), Campbell and his co-workers [19] studied the effect of selenium dioxide on eucarvone (1) and α-dihydroeucarvone (12). The alternative structure (12a) for the latter compound has been rejected as a result of certain recently accumulated evidence, which is described in detail at a later stage of this discussion.

From α-dihydroeucarvone (12), the above authors isolated two isomeric hydroxy-ketones, (45) and (46), of quite widely differing physical properties. The structure of (45) was deduced from spectroscopic data, and from its facile conversion to the corresponding enedione (47) with manganese dioxide. Ozonolysis and oxidation of the product afforded β,β-dimethylglutaric acid, while dehydration under mild conditions gave eucarvone.

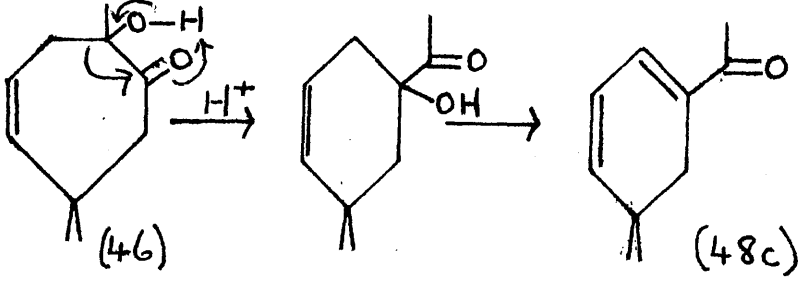
The structure of the isomeric hydroxy-ketone (46) was established on the basis of the spectroscopic evidence and a number of oxidative degradations. This compound was inert to manganese dioxide, but consumed one mole of periodic acid, thus establishing the vicinal relationship of the two oxygen functions. The hydroxy-ketone was unaffected by bismuth oxide, but yielded α,α-dimethylsuccinic acid on permanganate oxidation. Dehydration under mild conditions afforded not eucarvone, but an isomer of closely similar physical properties. The tetrahydro-derivative of

the new dehydration product was not identical with tetrahydroeucarvone (15), indicating that a skeletal rearrangement had occurred on dehydration, and thereby excluding the exocyclic methylene analogue of eucarvone (48a) from the list of possible products. Campbell and his collaborators also considered the dienone (48b), derived from a transannular methyl-migration as shown:-



However, direct comparison of the known tetrahydro-ketone from (48b) with the tetrahydro-ketone prepared above ruled out (48b) as the structure of the dehydration product.

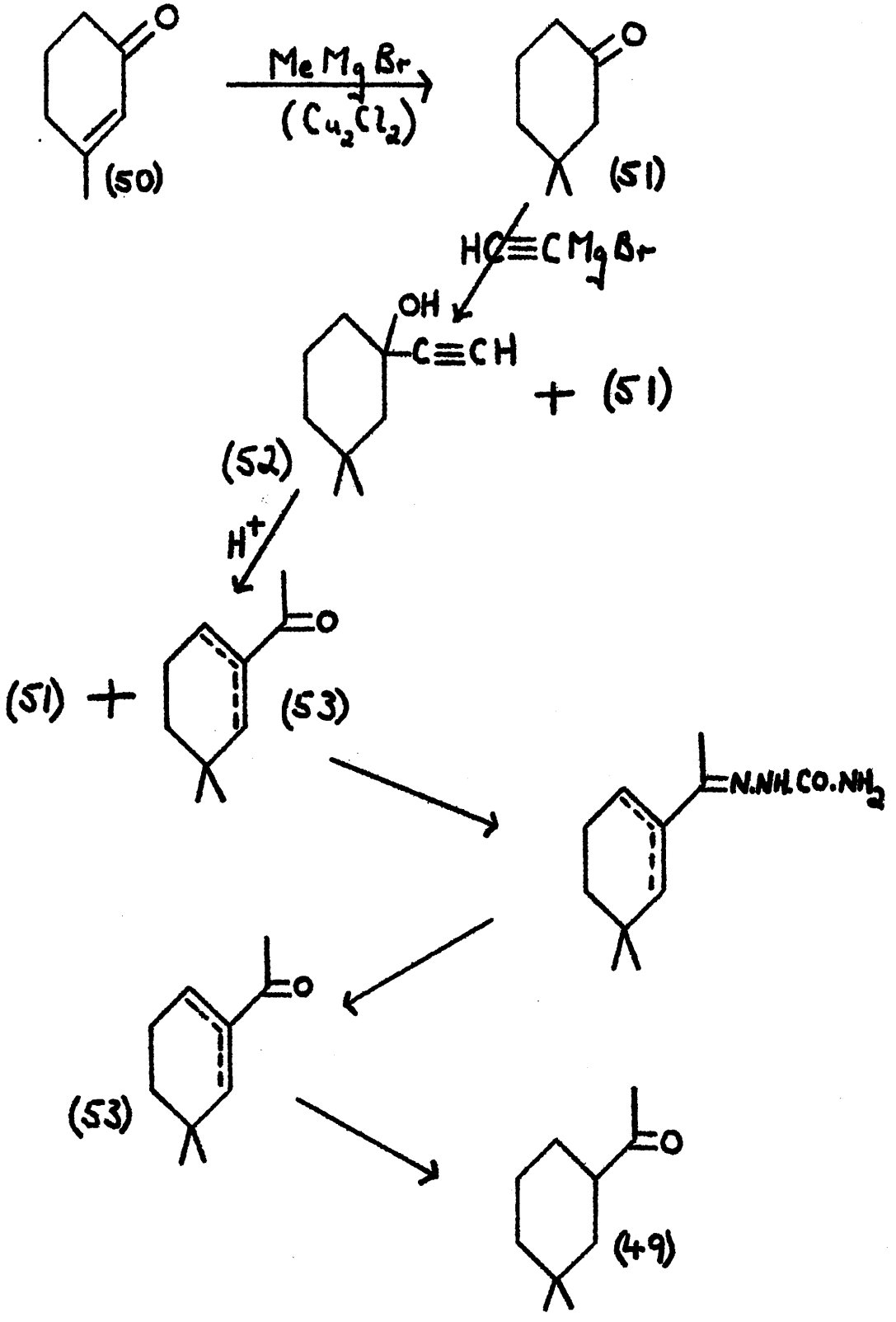
A further feasible mechanism for the dehydration, which bears analogies to the D-homosteroid ring en-largement, is outlined below:-



It was with a view to confirming this hypothesis that the syntheses of 1-acetyl-5,5-dimethylcyclohexa-1,3-diene (48c) and the corresponding saturated derivative (49), described in the following pages, were undertaken.

In an attempt to establish the skeletal structure of the dehydration product obtained by Campbell and his co-workers,[19] 1-acetyl-3,3-dimethylcyclohexane (49) has been synthesized from 3-methylcyclohex-2-en-1-one (50). The latter was converted into 3,3-dimethylcyclohexanone (51) by the action of methylmagnesium bromide in the presence of cuprous chloride[27]. Treatment of 3,3-dimethylcyclohexanone with ethynylmagnesium bromide[28] afforded the expected acetylenic carbinol (52), together with considerable quantities of starting material. Fractionation of these two compounds proved rather difficult, while attempts to remove the ketone by forming its semicarbazone served merely to increase the proportion of ketone present in the mixture by a reversal of the acetylenic addition reaction.

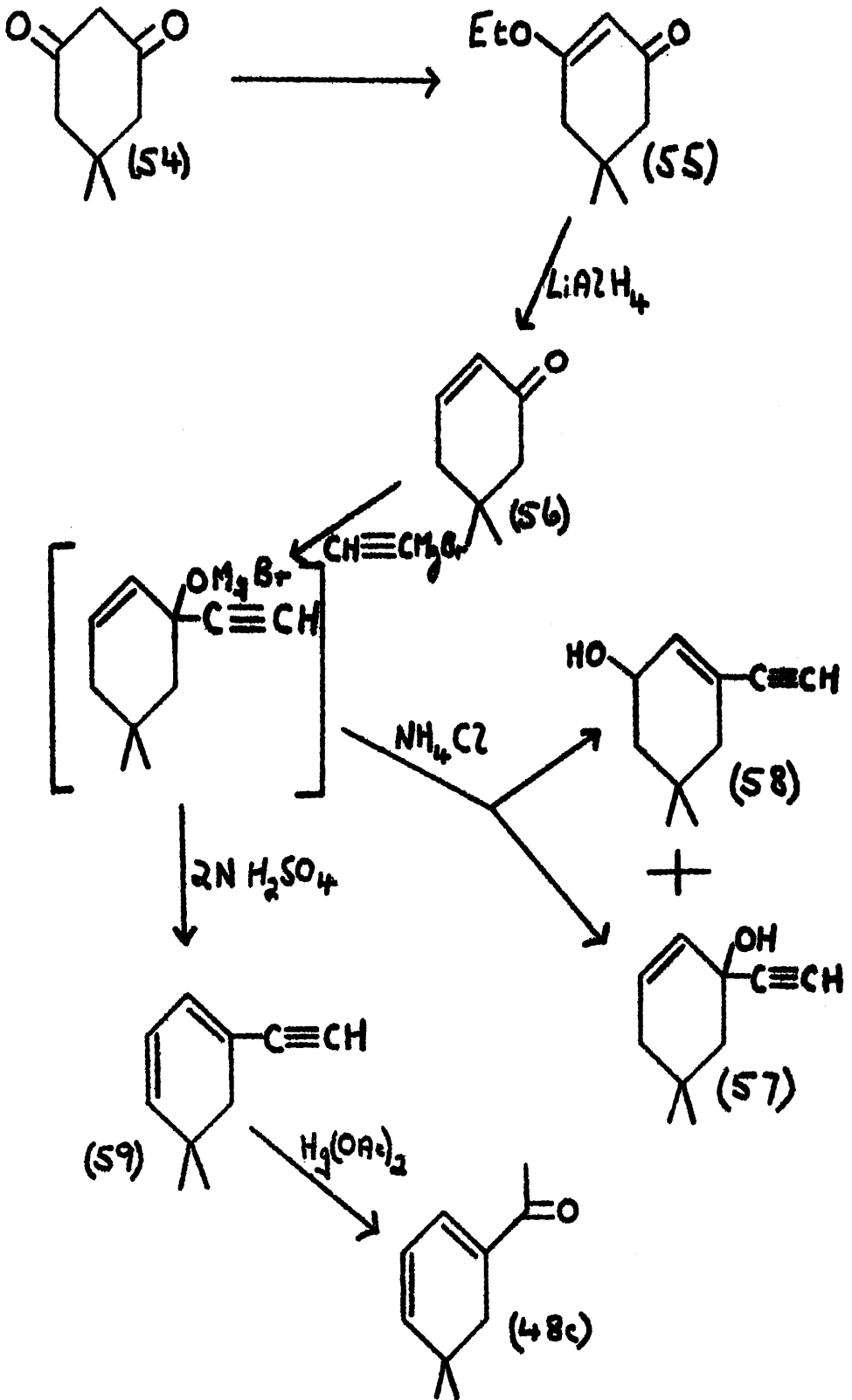
It was decided to carry the mixture forward to the next stage which involved refluxing with 90% formic acid[29] to convert the acetylenic carbinol to 1-acetyl-5,5-dimethylcyclohexene (53a or b). Fortunately, this unsaturated ketone proved to be readily separable from the saturated 3,3-dimethylcyclohexanone as its semicarbazone derivative. Regeneration of the parent 1-acetyl-5,5-dimethylcyclohexene from the semicarbazone[30], followed by catalytic hydrogenation over palladium-charcoal afforded 1-acetyl-3,3-dimethylcyclohexane (49) as its 2:4-dinitrophenylhydrazone. Although no direct


MeMgBr
(Cu2Cl2)
(50)
(51)
HC≡CMgBr
OH
C≡CH
+ (51)
(52)
H+
(51) +
(53)
N.NH.CO.NH2
(53)
(49)

comparison was available, this derivative compared favourably in melting-point and spectral properties with the derivative of the tetrahydro-ketone obtained by Campbell and his co-workers.

In view of the encouraging result obtained from the synthesis of 1-acetyl-3,3-dimethylcyclohexane (49), it was decided to attempt the synthesis of the corresponding dienone (48c), which was believed to represent the structure of Campbell's dehydration product. For this purpose, dimedone (54) was converted into its ethyl enol-ether (55)[31], which was then converted by reduction with lithium aluminium hydride into 5,5-dimethylcyclohex-2-en-1-one (56). This conjugated ketone was then treated with ethynylmagnesium bromide[28] - the product being worked-up under slightly acidic conditions. The effect of this treatment was not only to rearrange the initially-formed acetylenic carbinol (57) to the conjugated enyne (58), but also to effect the dehydration of (58) to the dienyne (59). Hydration of this conjugated acetylene with mercuric acetate[32] afforded the expected ketone (48c), again isolated as its 2:4-dinitrophenylhydrazone. This derivative was similar in colour, melting-point and spectral properties to the derivative obtained by Campbell from his dehydration product.

One obvious drawback to the above synthetic approach, however, lay in the lack of confirmation of the intermediate compounds, since mixtures of the conjugated and unconjugated hydroxy-enynes, (57) and (58), were

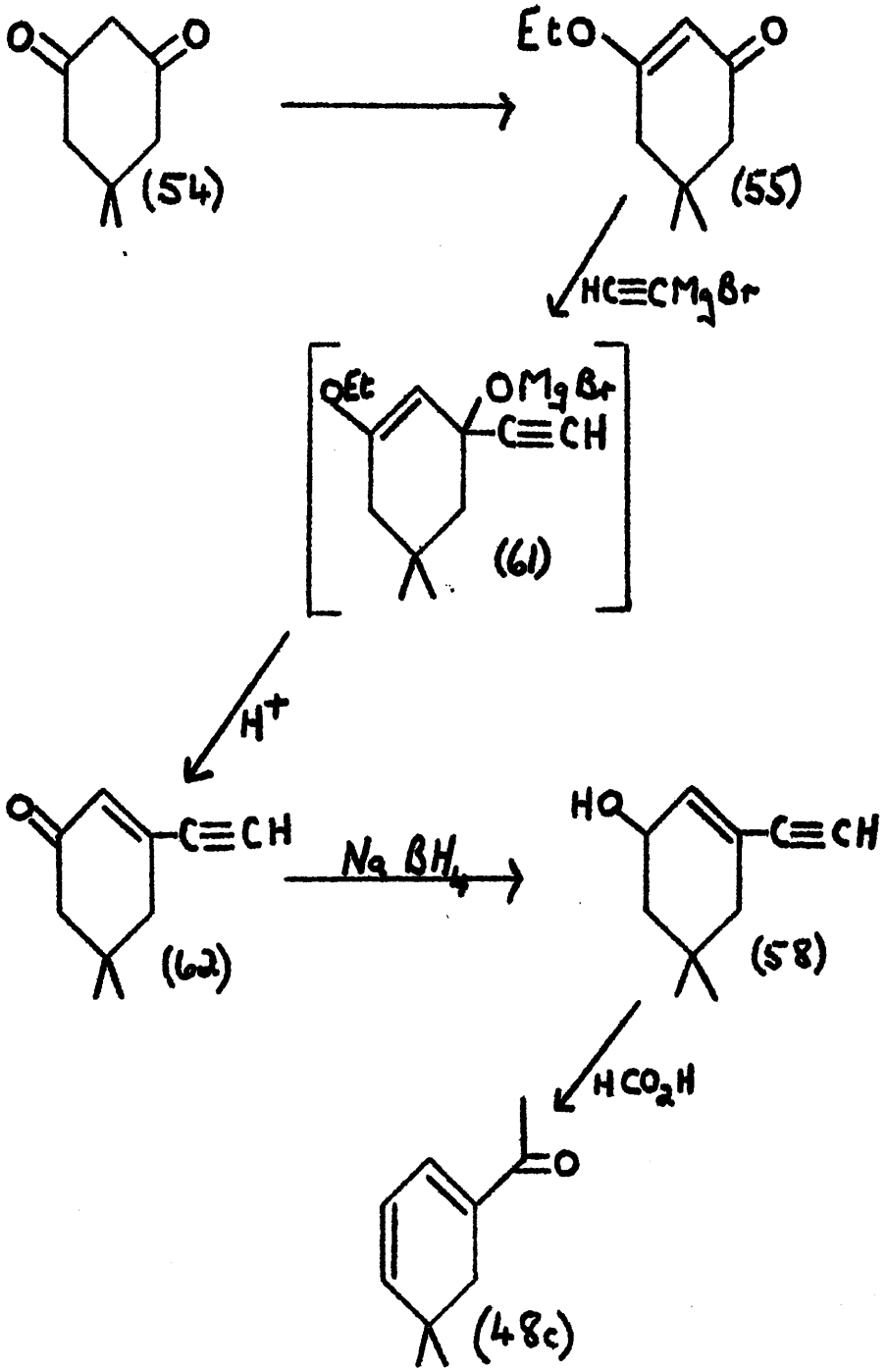

(54)
EtO
(55)
LiAlH4
(56)
CH≡CMgBr
OMgBr
C≡CH
NH4Cl
HO
C≡CH
(58)
+
OH
C≡CH
(57)
2N H2SO4
C≡CH
(59)
Hg(OAc)2
O
(48c)

obtained from the acetylenic Grignard reaction, even when the mildest conditions of working-up were employed. Some fractionation of these two compounds was possible, and both fractions afforded the same hydroxy-enone (60) on hydration of the triple bond under the conditions employed in the original method.

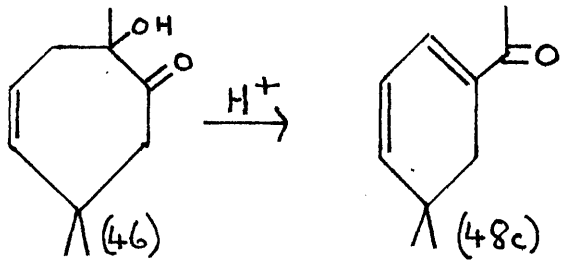
An unambiguous route to the desired acetylcyclohexadiene derivative (48c) again utilized dimedone (54) as its starting-point. Treatment of the ethyl enol-ether (55) of dimedone with ethynylmagnesium bromide in the usual way[28] afforded the acetylenic carbinol (61). This compound was converted into 3-ethynyl-5,5-dimethylcyclohex-2-en-1-one (62) on mild acid treatment[33]. The poor yield of the enynone (62) obtained by this means was attributed to the fact that the enol-ether used for the acetylenic addition reaction is a vinylogous carboxylic ester. This results in a deactivation of the carbonyl group towards Grignard and other nucleophilic reagents.

The conjugated enynone (62) was reduced with sodium borohydride to yield the corresponding secondary alcohol (58), which was converted on refluxing in 90% formic acid[29] to the desired 1-acetyl-5,5-dimethylcyclohexa-1,3-diene (48c). The 2:4-dinitrophenylhydrazone of this ketone was identical (melting-point, mixture melting-point, and infra-red) with the 2:4-dinitrophenylhydrazone of Campbell's dehydration product, prepared by repeating his experiments.

In face of the evidence accumulated by the aforementioned synthetic work, we are of the opinion that


(54)
EtO
(55)
HC≡CMgBr
OEt
OMgBr
C≡CH
(61)
H+
C≡CH
(62)
NaBH4
HO
C≡CH
(58)
HCO2H
O
(48c)

the dehydration product of the hydroxy-ketone (46) is the ring-contracted dienone (48c), i.e.,



The exact location of the double bond in α-dihydroeucarvone, (12) or (12a), has proved to be rather difficult, and some of the work we have carried out with this end in view is now described. The most convenient preparation of this ketone involves the sodium in alcohol reduction of eucarvone (1),[6] which affords dihydroeucarveol, (11) or (11a). Oxidation of dihydroeucarveol with chromium trioxide in acetone at 20° gives α-dihydroeucarvone, (12) or (12a), in good yield.

The position of the double bond in dihydroeucarveol, and, consequently, in α-dihydroeucarvone, depends on whether the sodium in alcohol reduction of eucarvone proceeds by an initial 1,4-addition of hydrogen, giving compound (11), or by a 1,6-addition, giving compound (11a).

A number of oxidative procedures were carried out in an attempt to locate the double bond in α-dihydroeucarvone. The ketone was unaffected by monoperphthalic acid, while peracetic acid yielded a product whose infra-red spectrum indicated the presence of considerable quantities of

a lactone, derived from Baeyer-Villiger oxidation of the carbonyl group. Performic acid gave a complex mixture of hydroxy-ketones, and ozonolysis afforded an oil from which no pure compound could be isolated.

In view of the unsatisfactory results of the usual oxidative procedures, a number of isomerization experiments were carried out. It was of interest to prepare the dioxolan of α-dihydroeucarvone, and to compare it with that of β-dihydroeucarvone (29), since the derivative of the conjugated ketone (63) should possess a double bond in the βγ-position, as should the dioxolan of α-dihydroeucarvone with structure (12a). Unfortunately, no dioxolan free from ketonic material could be obtained from α-dihydroeucarvone, and it was decided to study the effect of acid and base upon the ketone itself.

Prolonged refluxing of α-dihydroeucarvone with potassium acetate in dry ethanol[34] yielded a mixture of α- and β-dihydroeucarvone. The amount of the latter compound present in the mixture was estimated by ultra-violet absorption measurements to be 17%. This figure was not increased by prolonging the reaction. By analogy with the work of Campbell and his collaborators[19], we attempted to convert α-dihydroeucarvone into the conjugated isomer by refluxing it for a short period with ethanolic sulphuric acid. After 30 minutes the amount of conjugated ketone present was 25%. After 8 hours this value had increased only slightly to 27%.

In short, it would appear from the chemical evidence obtained, that α-dihydrocucarvone consists of a mixture of the βγ-unsaturated ketone (12) and the αβ-unsaturated ketone (12a). The former compound, which would be expected to undergo prototropic rearrangement to the conjugated ketone very slowly, if at all, is present in proportion to the αβ-unsaturated ketone, in the ratio of about 3 to 1. This conclusion was apparently vindicated by vapour-phase chromatography, which indicated that the so-called α-dihydrocucarvone consists of two major components present in the above proportion.

It might have been anticipated that α-dihydrocucarvone, like other similar ketones studied by Cookson[35], and by Labhart and Wagnière[36], would show some enhancement in the intensity of the ultra-violet absorption associated with the saturated carbonyl group. In fact, this phenomenon is not observed, as the intensity measurement for such a peak is almost identical with that for the saturated ketone, tetrahydrocucarvone (15). This may be due to the fact that neither of the structures, (12) or (12a), is sufficiently rigid to adopt the conformation necessary for interaction between the π-electrons of the double bond and those of the carbonyl group.

In an attempt to confirm the above conclusions concerning the structure of α-dihydrocucarvone drawn from purely chemical evidence, it was decided

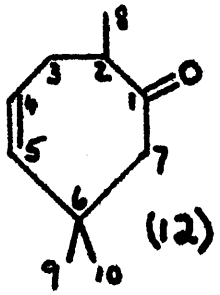
to investigate the structure of this ketone, prepared as previously described, by nuclear magnetic resonance methods. Both dihydroeucarveol, (11) or (11a), and α-dihydroeucarvone, (12) or (12a), have been studied by this method.

The results of a nuclear magnetic resonance study of the former were rather difficult to interpret in view of the more complex system of protons in dihydroeucarveol. Briefly, however, no evidence for the structure (11a) was obtained, while the spectrum was consistent with formula (11).

In the case of α-dihydroeucarvone, the spectrum in the allylic proton region (τapprox. 8.0) was too complex to establish whether there were two allylic protons present, as in structure (12), or three, as in structure (12a). However, no definite evidence for the grouping $>C = \overset{|}{C} - \underline{CH}(CH_3)$. $\overset{|}{C} = O$ was found, and so, if such a structure is present in α-dihydroeucarvone, it is certainly in minor amount.

The methylic proton region (τapprox. 8.9) showed four peaks of medium intensity, indicative of coupling of the C_8-methyl protons with <u>two</u> other protons, consistent with either structure, and a very strong singlet, representative of the <u>gem</u>-dimethyl group, which is not resolved.

Finally, a close study of the olefinic proton region (τapprox. 4.5) revealed a strong doublet, which arose from the coupling of the C_5-proton with the C_4-proton, and 4 weak doublets of equal intensity arising from



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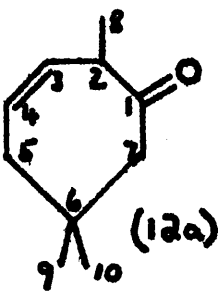
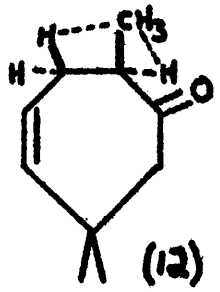


(12a)



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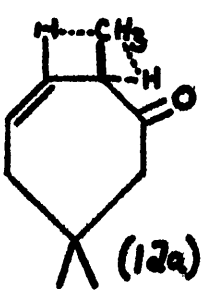

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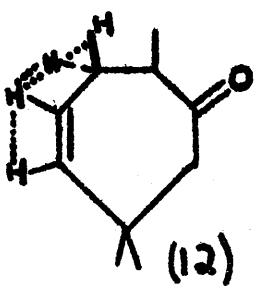

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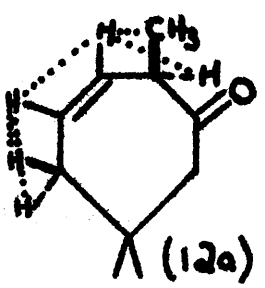


(12a)

the coupling of the C_4-proton with the C_5-proton, and with the two C_3-protons in the allylic position. This evidence was consistent with structure (12), whereas structure (12a) should exhibit an even more complex olefinic proton region, for which we could find no evidence[37].

The results of these nuclear magnetic resonance studies are completely consistent with our previous conclusion that α-dihydroeucarvone is in fact a mixture, in which structure (12) is the major, and structure (12a) the minor, component.

It was noted that, in the course of sodium in alcohol reduction of eucarvone, an intense violet colouration was produced initially, which gradually disappeared as the reduction proceeded. Accordingly, an attempt has been made to isolate any interesting self-condensation products which may be derived by treating eucarvone with hot methanolic potassium hydroxide solution. After 4 hours, a viscous yellow gum was obtained, from which traces of monomer were removed by steam-distillation. The high-boiling liquid so obtained had a molecular weight of around 300. This fact, taken in conjunction with the analytical data, indicated that the product was in fact a dimer, or a mixture of dimers.

The crude dimer absorbed 2 moles of hydrogen and contained two saturated carbonyl groups. Unfortunately, attempts to isolate crystalline material from this product by chromatography have been unsuccessful, as have attempts to prepare any of the usual

carbonyl, or active-methylene, derivatives. This would indicate a high degree of steric hindrance of the carbonyl functions. Vapour-phase chromatography of the crude dimer has shown the presence of two major components, in the ratio of around 4 to 1.

EXPERIMENTAL

Preparation of 3,3-dimethylcyclohexanone (51) - Methylmagnesium bromide was prepared from methyl bromide (34.0 g., 0.36 m.) and magnesium (7.2 g., 0.30 m.) in dry ether (190 ml) at 0°. To ensure complete reaction, the temperature was raised after 1 hour to 35°, and the solution refluxed gently for a further 30 minutes. After cooling the solution to 20° a catalytic quantity (2 mole %) of freshly prepared cuprous chloride was added, and the solution, which was now very dark in colour, was stirred at this temperature for 30 minutes. Further cooling to around 5° was necessary before adding a solution of 3-methylcyclohex-2-en-1-one (50) (25.0 g., 0.23 m.) in dry ether (75 ml.) over a period of 20 minutes. The temperature was then allowed to rise slowly, and the reaction completed by refluxing for 1 hour. The reaction mixture was then cooled, poured on to ice, and stirred with 15% hydrochloric acid. Removal of the ethereal layer, washing (sodium hydrogen carbonate, water), and drying (magnesium sulphate) afforded on evaporation and distillation the desired ketone, b.p. 180-182° (13.0 g., 48%). The infra-red spectrum showed $\nu_{max.}$ 1710, 1375, 1360 $cm.^{-1}$. Small amounts of the conjugated diene to be expected from the acid-catalyzed dehydration of the "normal" 1,2-addition product, and a considerable high-boiling residue, were also obtained.

The ketone so obtained formed a semicarbazone derivative, m.p. 193-6° (95% ethanol).

(Found: C, 58.96; H, 9.08; N, 23.10. $C_9H_{17}ON_3$ requires C, 58.98; H, 9.35; N, 22.95%).

1-Ethynyl-3,3-dimethylcyclohexan-1-ol (52) - Ethylmagnesium bromide was prepared from magnesium (3.9 g., 0.16 m.) and ethyl bromide (18 g., 0.17 m.) in dry tetrahydrofuran (110 ml.). A further quantity of tetrahydrofuran (80 ml.) was then saturated with acetylene, passage of which was continued during the addition of the ethylmagnesium bromide solution over a period of 45 minutes at 20°, under nitrogen. The resulting grey solution was cooled to 0°, the passage of acetylene stopped, and a solution of 3,3-dimethylcyclohexanone (12.0 g., 0.095 m.) in dry tetrahydrofuran (150 ml.) was added over a period of 1 hour. The solution was allowed to warm up to 20° and stirred overnight. Decomposition of the Grignard complex with ammonium chloride, extraction with methylene chloride, and drying, gave on evaporation and fractionation a main cut (9.4 g.), b.p. 86-96°/13 mm. containing what was obviously a mixture of the expected acetylenic carbinol (52) and 3,3-dimethylcyclohexanone. The infra-red spectrum of the mixture showed $\nu_{max.}$ 3450, 3350, 2140, 1710 $cm.^{-1}$

Attempts to separate the mixture by the use of excess semicarbazide reagent yielded considerable quantities of a semicarbazone, m.p. 190-191°, undepressed on admixture with the semicarbazone of 3,3-dimethylcyclohexanone. Re-investigation of the infra-red spectrum of the liquid mixture after this treatment showed the presence of relatively more ketone

than before.

An attempt to carry out the ethynylation reaction using sodium acetylide in liquid ammonia gave an essentially similar result.

1-Acetyl-3,3-dimethylcyclohexene (53a or b) - The mixture (7.5 g.) of compounds (51) and (52) obtained by the above method was refluxed in 90% formic acid (60 ml.) for 1 hour, before pouring into a mixture of ice and sodium carbonate. The usual processing afforded a mixture (4.0 g.) b.p. 80-90°/13 mm. The infra-red spectrum of this material had ν max. 1715, 1680, 1650, 1375, 1360 cm.$^{-1}$. Treatment of the mixture with excess semicarbazide hydrochloride in sodium acetate afforded on warming and shaking for 3 minutes, a white solid, m.p. 209-211° on recrystallization from ethanol. (Found: C, 63.14; H, 8.81; N, 20.22. $C_{11}H_{19}ON_3$ requires C, 63.17; H, 9.09; N, 20.29%). The ultra-violet spectrum showed λ max 261 mμ (log ε, 4.27).

Addition of water to the mother liquors, or prolonged cooling, gave the substantially pure semicarbazone of 3,3-dimethylcyclohexanone (51).

The semicarbazone of 1-acetyl-3,3-dimethylcyclohexene (0.25 g.) was steam-distilled from an aqueous solution of oxalic acid. Extraction of the steam-volatile material with ether in the usual way gave the parent ketone (0.10 g., 50%) b.p. 90-95°/13 mm. n_D^{18} 1.4805. νmax. 1680, 1650, 1365, 1355, 845 cm.$^{-1}$.

The semicarbazone was also converted directly to the 2:4-dinitrophenylhydrazone by boiling with an

excess of the reagent in ethanolic sulphuric acid. Scarlet platelets, m.p. 159-160° on recrystallization from 95% ethanol. (Found: C,58.05; H,6.26; N,16.60. $C_{16}H_{20}O_4N_4$ requires C, 57.82; H, 6.07; N,16.87%). λ max ($CHCl_3$) 382 mμ (log ε,4.41).

1-Acetyl-3,3-dimethylcyclohexane (49) - Attempts to catalytically reduce 1-acetyl-3,3-dimethylcyclohexene (53a or b) to the saturated ketone using palladium-charcoal were unsuccessful. However, hydrogenation took place rapidly and smoothly over platinum oxide in ethanol. The product was isolated as its 2:4-dinitrophonylhydrazone, m.p. 118-120° on re-crystallization (pale orange needles) from petrol (b.p. 80-100°). (Found: C,57.62; H,6.24; N,16.84. $C_{16}H_{22}O_4N_4$ requires C,57.47; H,6.63; N, 16.76%). λ max. ($CHCl_3$) 366 mμ (log ε, 4.36). The 2:4 dinitrophonylhydrazone of Campbell's[19] tetrahydro-ketone has m.p. 115-118°, λ max ($CHCl_3$) 364 mμ (log ε ,4.34).

Dimedone (Ethyl) Enol-ether (55) - Dimedone (54) (38.5 g.) and ethanol (50 ml.) were refluxed in benzene (300 ml.), in the presence of p-toluenesulphonic acid (0.5 g.). The water evolved was collected in a Dean-Stark separator and the reaction was complete in 4 hours. The reaction mixture was then cooled, washed (sodium carbonate, water), and dried (magnesium sulphate). The product was purified by distillation, b.p. 138-140°/12 mm. but solidified rapidly to a

white crystalline material, m.p. 58° (35.6 g. 82%).
$\nu_{max.}^{Nujol}$ 1655, 1615, 1035 cm.$^{-1}$

5,5-Dimethylcyclohex-2-en-1-one (56) - To a slurry of lithium aluminium hydride (2.0 g., 0.06 m.) in dry ether (50 ml.) was added with stirring, over a period of 3 minutes, a solution of dimedone enol-ether (18.7 g; 0.11 m.) in ether (70 ml.). The suspension was stirred for 1 hour at 20°, before destroying the excess hydride with an ethereal solution of ethyl acetate. The reaction mixture was poured into 2N sulphuric acid and the product isolated in the usual way by distillation, b.p. 61-66°/11 mm. (9.4 g. 68%).

The 2:4-dinitrophenylhydrazone formed orange needles, m.p. 160° on recrystallization from ethanol. (Found: C, 55.08; H, 5.16. $C_{14}H_{16}O_4N_4$ requires C, 55.25; H, 5.30%).

1-Ethynyl-5,5-dimethylcyclohexa-1,3-diene (59) - Ethylmagnesium bromide, prepared under nitrogen from magnesium (2.4 g. 0.1 m.) and ethyl bromide (11.0 g; 0.1 m.) in dry tetrahydrofuran (70 ml.), was added to a saturated solution of acetylene in tetrahydrofuran (80 ml.) through which acetylene was passed until all the Grignard reagent had been added. The solution of the acetylenic Grignard reagent was then cooled to 0° before adding a solution of 5,5-dimethylcyclohex-2-en-1-one (56) (9.6 g., 0.08 m.) in tetrahydrofuran (100 ml.). After stirring for 16 hours under nitrogen, the Grignard complex was decomposed with ice-cold 2N sulphuric acid. Extraction with methylene chloride gave on evaporation and distillation only a

small amount (0.7g.) of a colourless liquid, b.p. 45-50°/16 mm. n_D^{25} 1.4954 ν_{max} 3260, 2077 cm.$^{-1}$ λ_{max} 295 mμ (log ε, 3.74). Microhydrogenation over platinum oxide in acetic acid was accompanied by the uptake of 3.6 moles of hydrogen. The liquid gave a heavy white precipitate with ammoniacal silver nitrate, but formed no derivative with 2:4-dinitrophenylhydrazine reagent. The absence of a hydroxyl group and the presence of an acetylenic function prompted us to the conclusion that this compound must be 1-ethynyl-5,5-dimethylcyclohexa-1,3-diene (59).

1-Acetyl-5,5-dimethylcyclohexa-1,3-diene (48c) - The conjugated dienyne (59) (28 mg.) was refluxed in 90% acetic acid (3.5 ml.) containing mercuric acetate (20 mg.) and a trace of sulphuric acid, for 45 minutes. Treatment of the reaction mixture with an ethanolic hydrochloric acid solution of 2:4-dinitrophenylhydrazine yielded a dark red derivative (9.5 mg.), m.p. 169° on recrystallization from ethanol. (Found: N,17.40. $C_{16}H_{18}O_4N_4$ requires N,16.95%). $\lambda_{max.}$ ($CHCl_3$) 399 mμ (log ε ,4.42).

The 2:4-dinitrophenylhydrazone of Campbell's[19] dehydration product has m.p. 172-173°. $\lambda_{max.}$ ($CHCl_3$) 396 mμ (log ε , 4.45).

1-Ethynyl-5,5-dimethylcyclohex-2-en-1-ol (57) and 3-ethynyl-5,5-dimethylcyclohex-2-en-1-ol (58)- When the acetylenic Grignard addition complex derived from 5,5-dimethylcyclohex-2-en-1-one (56) was worked-up under neutral conditions, using ammonium chloride, two liquid fractions were obtained on distillation, both

differing from the material isolated by employing 2N sulphuric acid. The lower boiling fraction (1.20 g.) b.p. 74-76°/11 mm. n_D^{25} 1.4750, had νmax. 3360, 2095 cm.$^{-1}$ λmax 227 mμ (log ε, 3.89). The higher boiling material (0.55 g.), b.p. 82-84°/11 mm. n_D^{25} 1.4828, had νmax. 3350, 2095 cm.$^{-1}$ The ultra-violet absorption spectrum showed no high-intensity maximum. Both fractions yielded precipitates with ammoniacal silver nitrate solution.

3-Acetyl-5,5-dimethylcyclohex-2-en-1-ol (60)

(a) The lower-boiling fraction obtained in the previous experiment was refluxed for 1 hour in 90% acetic acid containing mercuric acetate and a trace of sulphuric acid. Isolation of the resulting ketone as its 2:4-dinitrophenylhydrazone in the usual way afforded orange needles, m.p. 136° on recrystallization from ethanol. (Found: C, 55.08; H, 5.28; N, 15.90. $C_{16}H_{20}O_5N_4$ requires C, 55.17; H, 5.75; N, 16.09%). λmax. ($CHCl_3$) 382 mμ (log ε, 4.40). λmax. (EtOH), 376 mμ (log ε, 4.41).

(b) The higher boiling fraction from the previous experiment on treatment in the same way afforded a 2:4-dinitrophenylhydrazone as orange needles, m.p. 135° on recrystallization from ethanol. The melting-point was undepressed on admixture with the derivative obtained as described in method (a).

3-Ethynyl-5,5-dimethylcyclohex-2-en-1-one (62) - Dimedone ethyl enol-ether (55) (10.7 g., 0.064 m.), dissolved in dry tetrahydrofuran (50 ml.) was added over a period of 1 hour to a solution of ethynylmagnesium bromide in tetrahydrofuran (100 ml.), prepared from

magnesium (2.4 g. 0.099m.) and ethyl bromide (11.0 g., 0.10 m.) as already described. The passage of acetylene was then stopped, and the reaction mixture refluxed under nitrogen for 2 hours. 10% Sulphuric acid (10 ml.) was added and the mixture again refluxed under nitrogen for 1 hour. The usual processing afforded on distillation a pale yellow liquid (1.0 g., 11%), b.p. 62-64°/0.9 mm. n_D^{25} 1.5110. ν max. 3250, 2100, 1660, 1600, 1365, 1350 cm.$^{-1}$ λ max. 262 mμ (log ε, 4.21). This liquid gave a positive test for the -C ≡ CH grouping with ammoniacal silver nitrate.

3-Ethynyl-5,5-dimethylcyclohex-2-en-1-ol (58) - Reduction of the conjugated enynone (62) with excess sodium borohydride in methanol proceeded at 20° after initial slight warming to start the reaction. After 1 hour, the reaction mixture was poured into a large volume of water and extracted with methylene chloride. Washing with 4N sodium hydroxide, water, and drying (magnesium sulphate) gave on evaporation a light brown oil, ν max. 3300, 2095, 1630 cm.$^{-1}$ A test with ammoniacal silver nitrate solution for the -C ≡ CH grouping was positive.

1-Acetyl-5,5-dimethylcyclohexa-1,3-diene (48c) - The crude product from the borohydride reduction was refluxed for 1 hour in 90% formic acid. The crude ketone isolated by ether extraction was not distilled, but on treatment with an ethanolic, sulphuric acid solution of 2:4-dinitrophenylhydrazine yielded a dark red derivative. Purification on a Kieselguhr-Bentonite

column gave a single derivative, m.p. 174° on recrystallization from n-butanol as crimson needles. $\lambda_{max.}$ ($CH Cl_3$) 397 mμ (log ε, 4.43). The melting point was undepressed on admixture with a sample of the 2:4 dinitrophenylhydrazone of Campbell's dehydration product, prepared by repeating his experiments. The infra-red spectra of the two compounds were superimposable.

Dihydroeucarveol (11) - Eucarvone (15.0 g., 0.1 m.) was dissolved in ethanol (200 ml.), and sodium (23.0 g., 1.0 m.) was added as rapidly as possible. The solution was refluxed finally for 30 minutes to ensure complete dissolution of the sodium. (The reaction mixture was originally violet and passed through various shades of red before becoming almost colourless). The reaction mixture was poured into a large volume of water and steam-distilled rapidly. Ether extraction and drying (magnesium sulphate), followed by evaporation and distillation afforded dihydroeucarveol (10.4 g., 67%) as a colourless liquid, b.p. 108-110°/20 mm. n_D^{25} 1.4740.

Oxidation of dihydroeucarveol (11) to α-Dihydroeucarvone (12)

(a) Chromium trioxide (16.0 g., 0.16 m.) was added slowly with stirring to pyridine (170 ml.) cooled to 15°. The initial red colour gave way finally to a yellow slurry. A solution of dihydroeucarveol (10.0 g., 0.065 m.) in pyridine (100 ml.) was then added slowly at 20°. The solution was allowed to stand for 16 hours at this temperature before pouring into water and bubbling sulphur dioxide through the solution until a green colour

was obtained. Extraction with ether in the usual way gave α-dihydroeucarvone (3.3 g., 36%) as a colourless oil, b.p. 89-93°/15 mm., n_D^{25} 1.4635.

(b) - A solution of chromic acid which was 8N with respect to oxygen was prepared by dissolving chromium trioxide (26.7 g.) in conc. sulphuric acid (23 ml.) and water (40 ml.) and making up to 100 ml. Dihydroeucarveol (7.0 g., 0.045 mm.), dissolved in "Analar" acetone (20 ml.) was then titrated with the oxidizing mixture at 20° until a permanent brown colour was observed. After pouring into water and extraction with ether in the usual way, α-dihydroeucarvone (4.4 g., 63%) was obtained on distillation as a colourless liquid, b.p. 82-84°/13 mm., n_D^{20} 1.4671. λmax. 290 mμ (log ε, 1.54). Vapour-phase chromatography of the ketone on 5% Apiezon 'L' revealed the presence of two major components in amounts of 73% and 21%. The residual 6% was accounted for by three unspecified impurities, probably including a trace of dihydroeucarveol.

Oxidative experiments on α-dihydroeucarvone (12)

(a) α-Dihydroeucarvone (3.3 g., 0.22 m.) was treated with an ethereal solution of monoperphthalic acid (4.4 g., 0.24 m.) at 20° for 72 hours. After filtration of the phthalic acid produced, the solution was washed (sodium hydrogen carbonate, water), dried (magnesium sulphate) and distilled. Only one fraction was obtained, b.p. 80-85°/15 mm. The infra-red spectrum of this compound was identical with that of starting-material.

(b) - Peracetic acid solution (220 mg., 0.003 m.) was added slowly at 0° to α-dihydroeucarvone (330 mg., .002 m.). The mixture was allowed to stand at 20° for 16 hours before adding excess sodium meta-bisulphite and adjusting the pH to 8-9 with sodium hydroxide solution. Extraction with ether afforded a product whose infra-red spectrum had ν max. 3500, 1750, 1715 $cm.^{-1}$ This liquid gave no solid derivative on treatment with 2:4-dinitrophenylhydrazine in methanolic hydrochloric acid.

(c) - α-Dihydroeucarvone (750 mg., 0.005 m.) was dissolved in 98% formic acid and 30% hydrogen peroxide solution (1.1 ml.) added slowly with shaking. The mixture was warmed to 45° for 2 hours before removing most of the formic acid under reduced pressure. The residue was dissolved in a little methanol and refluxed for 15 minutes with 20% sodium hydroxide solution. The reaction mixture was cooled and poured on to ice and dilute hydrochloric acid. Extraction with ether gave on distillation a colourless liquid, b.p. 76-80°/0.08 mm. ν max. 3550, 1715, 1680, 1655. Treatment with a methanolic hydrochloric acid solution of 2:4-dinitrophenylhydrazine gave an oily product from which no solid derivative could be isolated.

(d) - α-Dihydroeucarvone (700 mg.) was dissolved in ethyl acetate (20 ml.) and ozonized at -70° until a permanent blue colour was observed (30 minutes). The ozonide was decomposed with alkaline hydrogen peroxide, acidified, and ether-extracted for 48 hours. The product obtained was acidic but yielded no pure compound.

Attempted preparation of the dioxolan of α-dihydroeucarvone (63) - The ketone (1.50 g., 0.01 m.) was refluxed in benzene in the presence of ethylene glycol (4.91 g., 0.08 m.) and p-toluenesulphonic acid (0.11 g.) for 4 hours. The solution was cooled, washed (sodium hydrogen carbonate, water), and dried (magnesium sulphate). The product was collected in four cuts boiling over the range 80-115°/15 mm. n_D^{24} 1.4721-1.4750. All fractions showed νmax. 1705 cm.$^{-1}$

Isomerization of α-dihydroeucarvone (12) to β-dihydroeucarvone (29)

(a) - α-dihydroeucarvone (0.44 g.) was refluxed in ethanol (25 ml.) containing fused potassium acetate (0.48 g.). After 20 hours the solution was cooled, evaporated to small volume, and extracted with a mixture of ethyl acetate and water. The ethyl acetate extract was dried and distilled b.p. 88-90°/15 mm. n_D^{22} 1.4672. λmax. 238 mμ (log ε, 3.02) - equivalent to a 17% conversion.

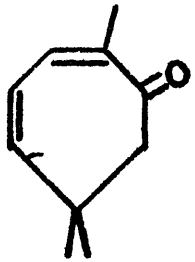
(b) The saturated ketone (2.0 g.) was refluxed in ethanol (20 ml.) containing sulphuric acid (0.5 ml.) under nitrogen for 30 minutes. The product on isolation in the usual manner and distillation, had b.p. 89-94°/13 mm. νmax. 1705, 1675 cm.$^{-1}$ λmax. 240 mμ (log ε, 3.25) - equivalent to a 25% conversion to β-dihydroeucarvone. On repeating the experiment with a reflux period of 8 hours, an essentially similar result was obtained.

The effect of methanolic potassium hydroxide on Eucarvone

Eucarvone (2.25 g.) was refluxed in 90% methanol containing potassium hydroxide (2.0 g.). A deep violet colour was produced immediately and persisted until, after 4 hours, the reaction mixture was cooled and poured into a large volume of water. Extraction with ether, washing (water), and drying (magnesium sulphate) afforded on evaporation a yellow gum, the odour of which indicated the presence of considerable quantities of eucarvone. Steam was passed through this gum for 30 minutes, and the product obtained on re-extraction and drying was a viscous liquid, b.p. 130-132°/0.13 mm. (Found: C, 79.97, H, 9.76. $(C_{10}H_{14}O)_2$ requires C, 80.00; H, 9.33%). Molecular weight (cryoscopic) approx. 305. νmax. 1710, 1655 cm.$^{-1}$ $\lambda_1$max. 282 mμ (log. ε , 2.58); $\lambda_2$max. 294 mμ (log ε ,2.57.) Careful chromatography on Grade I alumina gave no crystalline material. Vapour phase chromatography on 5% Apiezon 'L' indicated that the dimer contained two components, present in amounts of 62% and 38%.

Attempts to prepare a 2:4-dinitrophenylhydrazone, oxime, and semicarbazone were without success, as were attempted condensations with benzaldehyde or furfural.

Microhydrogenation of the dimer over 5% palladium-charcoal led to the uptake of 2.16 moles of hydrogen. The ketone so obtained had νmax. 1715 cm.$^{-1}$



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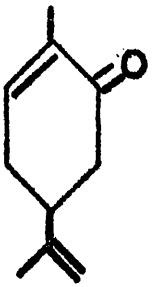

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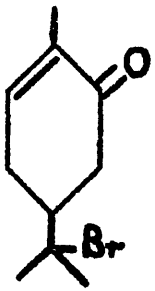

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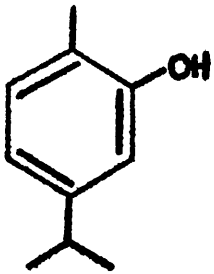

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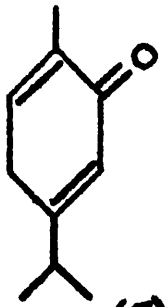

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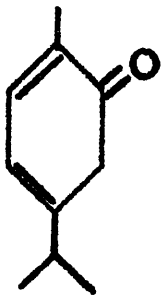

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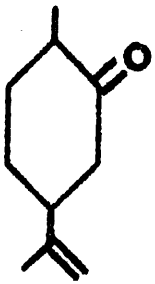

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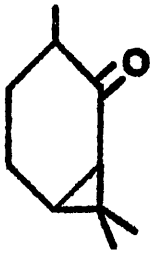

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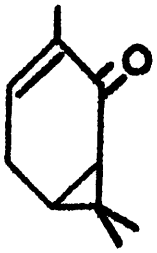

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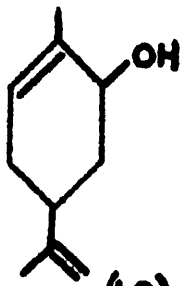

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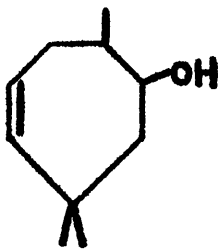

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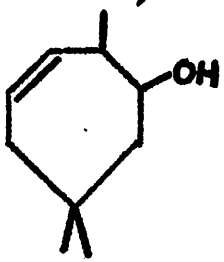

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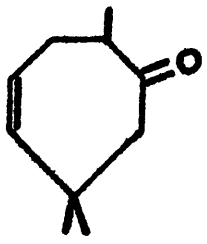

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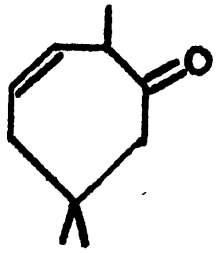

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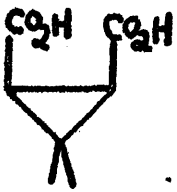

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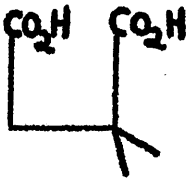

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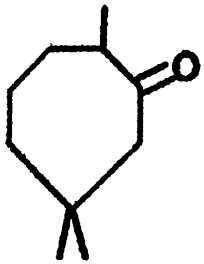

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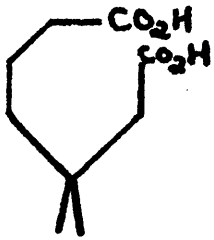

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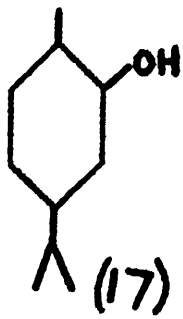

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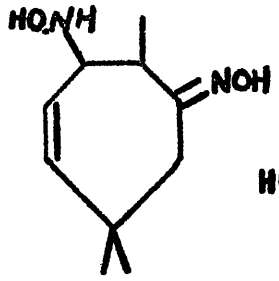

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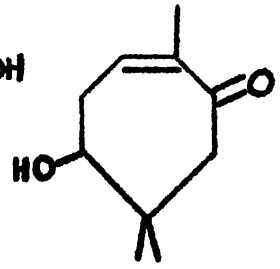

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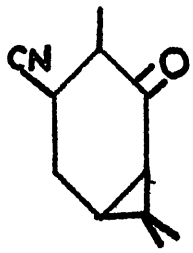

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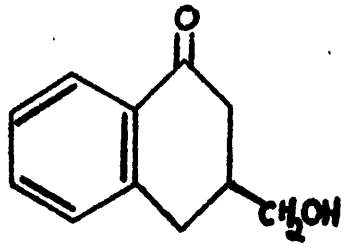

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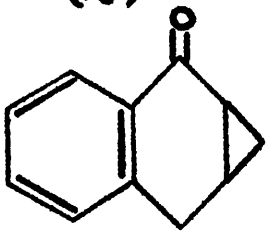

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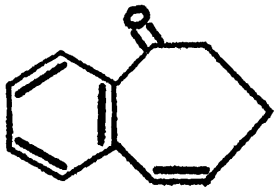

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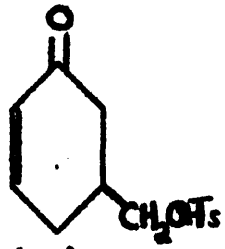

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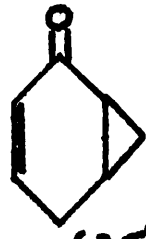

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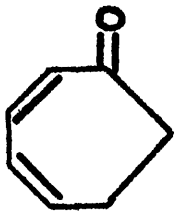

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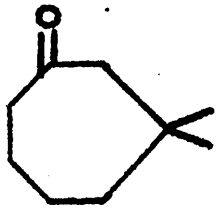

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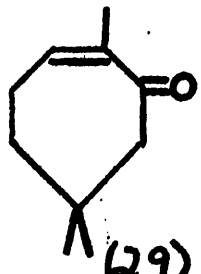

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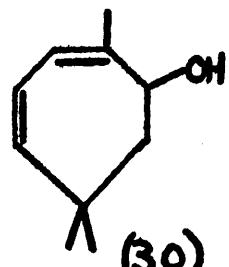

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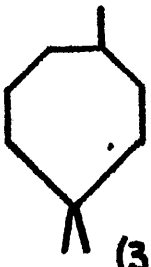

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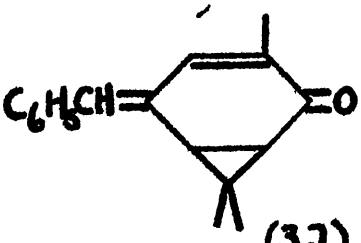

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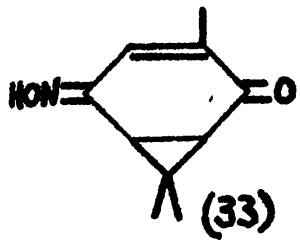

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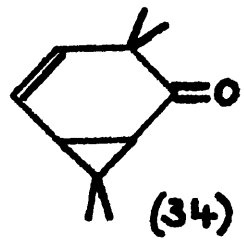

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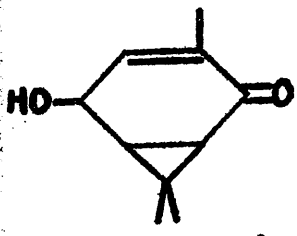

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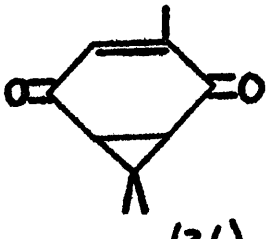

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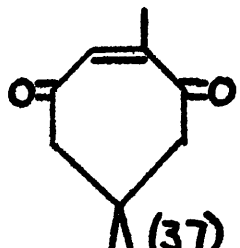

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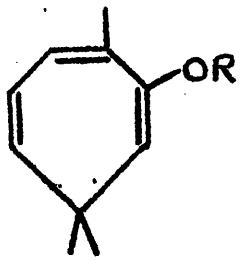

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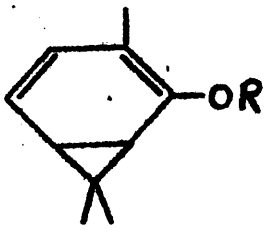

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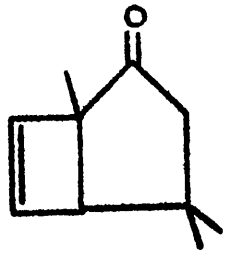

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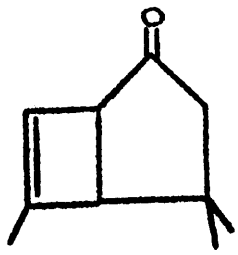

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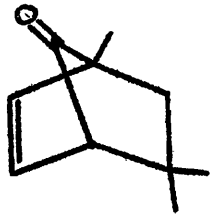

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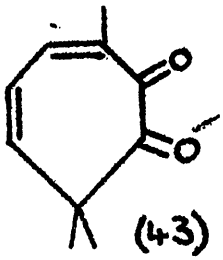

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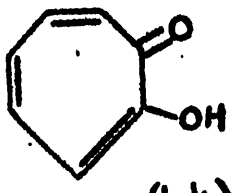

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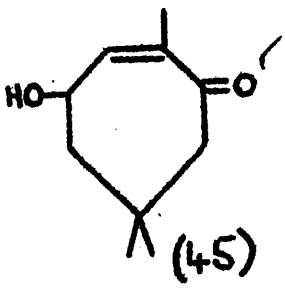

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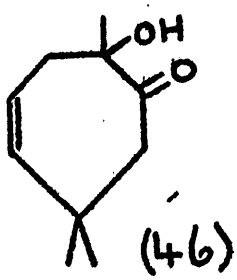

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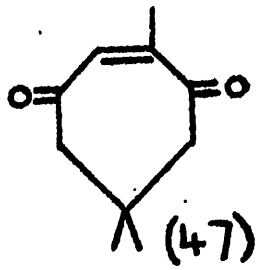

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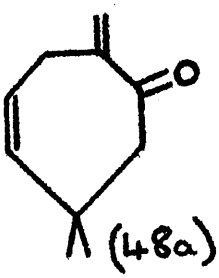

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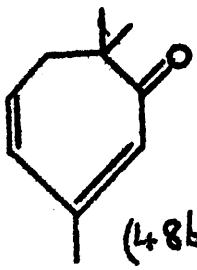

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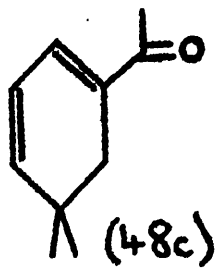

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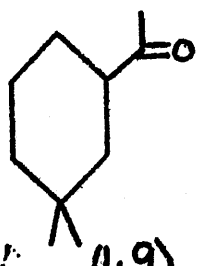

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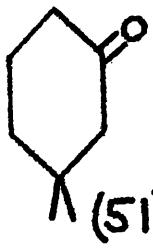

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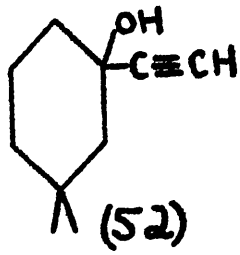

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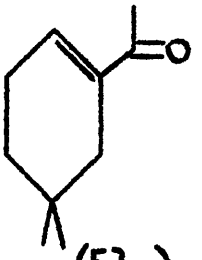
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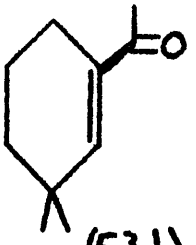
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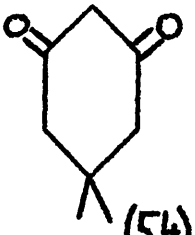
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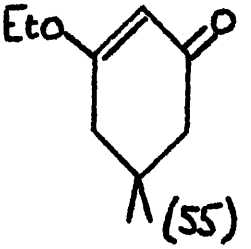
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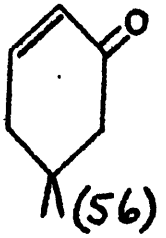
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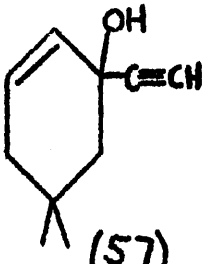
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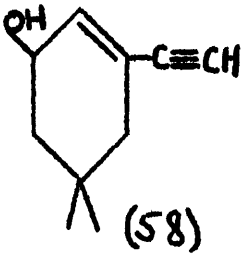
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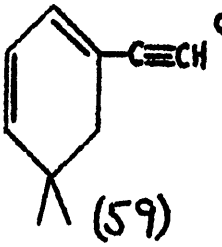
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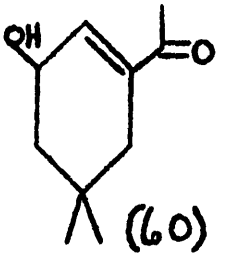
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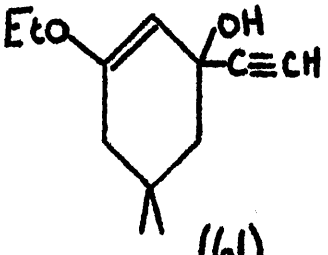
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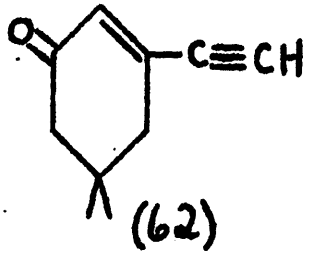
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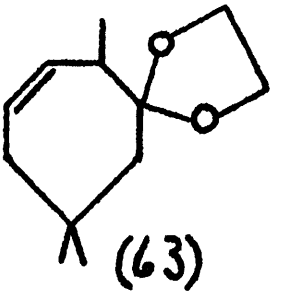
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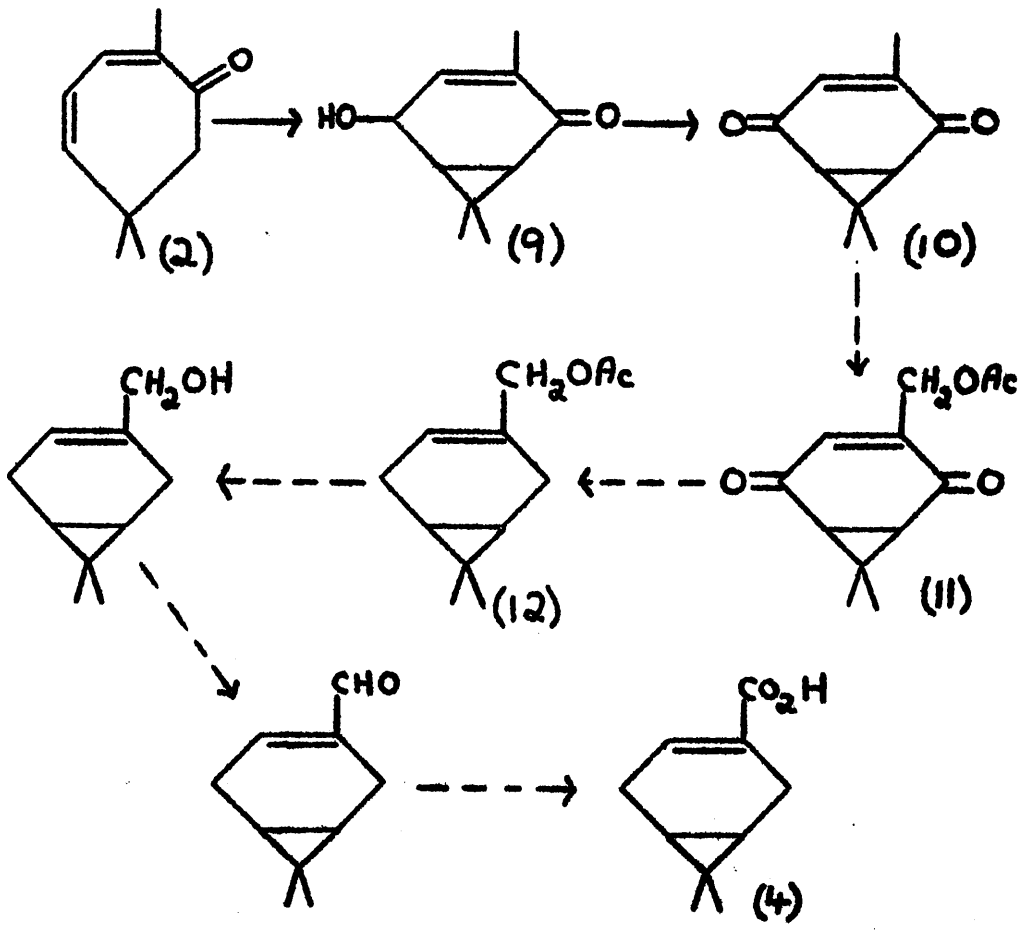
DISCUSSION

Attempts have been made to synthesize the interesting monoterpene, chamic acid, isolated by Erdtman and his co-workers[38] from the heartwood of Chamaecyparis nootkatensis, and of which no synthesis has so far been reported. Chamic acid has been shown by Erdtman[39] to possess the bicyclic structure (1). Our interest in this problem stemmed from the fact that chamic acid possesses the bicyclo(4:1:0) heptane skeleton, since, as described in the historical introduction, eucarvone (2) yields a variety of similar bicyclic derivatives,[22] and appears from physical measurements[21] to exist to a small extent in the bicyclic form (3).

A second compound, chaminic acid, isolated in minute quantities from C. nootkatensis was believed to have the structure (4). Chaminic acid is the optical antipode of iso-chamic acid, derived by alkaline isomerization of chamic acid (1). An attempt was made by Erdtman[39] to convert Δ^3-carene (5) into racemic iso-chamic acid (referred to hereafter simply as iso-chamic acid) by selenium dioxide oxidation to the aldehyde (6). A parallel reaction was the conversion of α-pinene (7) to myrtenal (8)[40], but in the case of Δ^3-carene oxidation took place preferentially at the methylenic sites adjacent to the double bond.

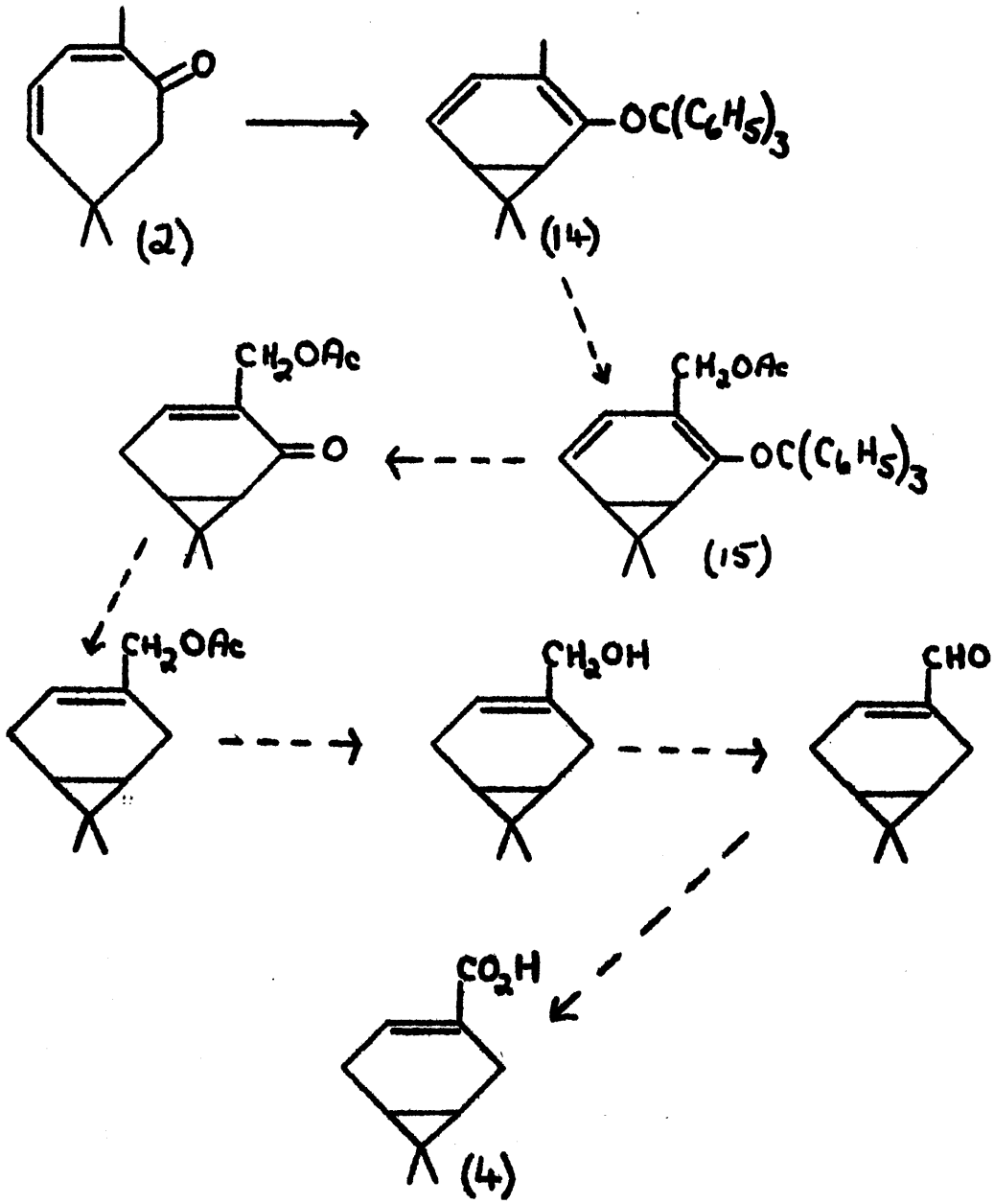
The first route by which we attempted to synthesize, initially, iso-chamic acid (4), involved the use of carenedione (10) as an intermediate. Corey and his collaborators[22] obtained carenolone (9) by oxidation of eucarvone (2) with selenium dioxide. Manganese dioxide


(2)
HO
(9)
(10)
CH2OH
CH2OAc
CH2OAc
(12)
(11)
CHO
CO2H
(4)

treatment of carenolone (9) then afforded carenedione (10), in 24% yield, based on eucarvone. We have found, however, that while the second step was virtually quantitative, a very poor yield of carenolone was obtained in the selenium dioxide oxidation. By employing the base-catalyzed nitrosation of eucarvone, also described by Corey[22], we obtained oximino-eucarvone (13), which was converted smoothly into carenedione (10) by deoximation with nitrous acid.[41] The yield of carenedione obtained by this method was 45%, based on eucarvone.

A considerable number of experiments have been carried out in an attempt to convert carenedione into some suitably oxygenated product such as (11). Lead tetraacetate and tert-butyl perbenzoate had no effect upon carenedione. N-Bromosuccinimide afforded a bromine-containing product, which gave a material with acetate absorption (1745 cm.), following metathesis with potassium acetate. This latter product was a mixture, however, and it was obvious that the N-bromosuccinimide had attacked at least two of the three activated allylic positions available. Accordingly, this synthetic approach, which depended very largely on the two steps (10) ⟶ (11), and (11) ⟶ (12), was abandoned.

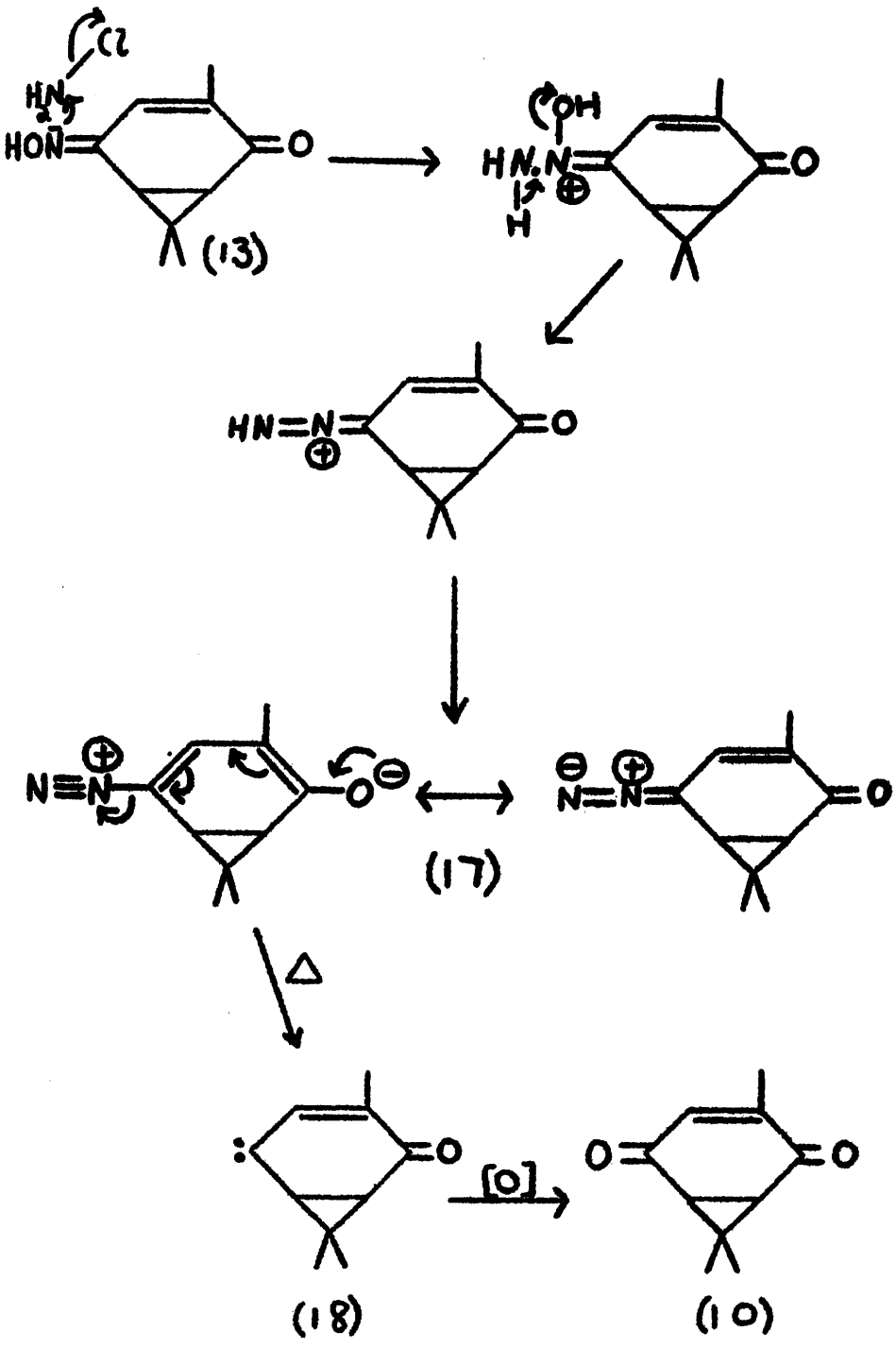
The second approach to the synthesis of iso-chamic acid (4) employed as intermediate the triphenylmethyl (trityl) enol-ether of eucarvone (14), recently reported by Conrow[42]. In this paper, Conrow has put forward convincing evidence, based principally on ultra-violet absorption and nuclear magnetic resonance data, for the formulation of the enol-ether as the bicyclic compound (14). This is the first reported preparation of a bicyclic enol-ether of eucarvone.


O
(2)
OC(C6H5)3
(14)
CH2OAc
O
CH2OAc
OC(C6H5)3
(15)
CH2OAc
CH2OH
CHO
CO2H
(4)

A wide range of reagents has been employed in an endeavour to prepare a suitable elaboration product of the above enol-ether, such as (15). The enol-ether was recovered unchanged from the reaction with tert-butyl perbenzoate, while lead tetraäcetate and mercuric acetate yielded only starting-material, and some triphenyl carbinol, formed by hydrolysis of the enol-ether. Selenium dioxide also afforded no useful product. N-Bromosuccinimide, followed by potassium acetate metathesis, gave a bromine-containing solid acetate derivative, with a molecular-weight in the region of 600. This again suggests non-selective attack of N-bromosuccinimide, and partial metathesis to yield a product such as (16). Since this route did not appear to offer any greater chance of success than the previous one, it too was abandoned.

The intermediate oximino-eucarvone (13) already referred to, has proved to be of considerable interest, for a number of reasons. In the first place, it appeared to afford a route to the corresponding diazo-ketone (17), which is a vinylogous α-diazo-ketone. A number of interesting rearrangements of cyclic α-diazo-ketones have recently been accomplished by Cava[43] and by Meinwald[44], and we felt that it would be of interest to prepare a vinylogous α-diazo-ketone, and to compare its reactions with those of the simple α-diazo-ketones.

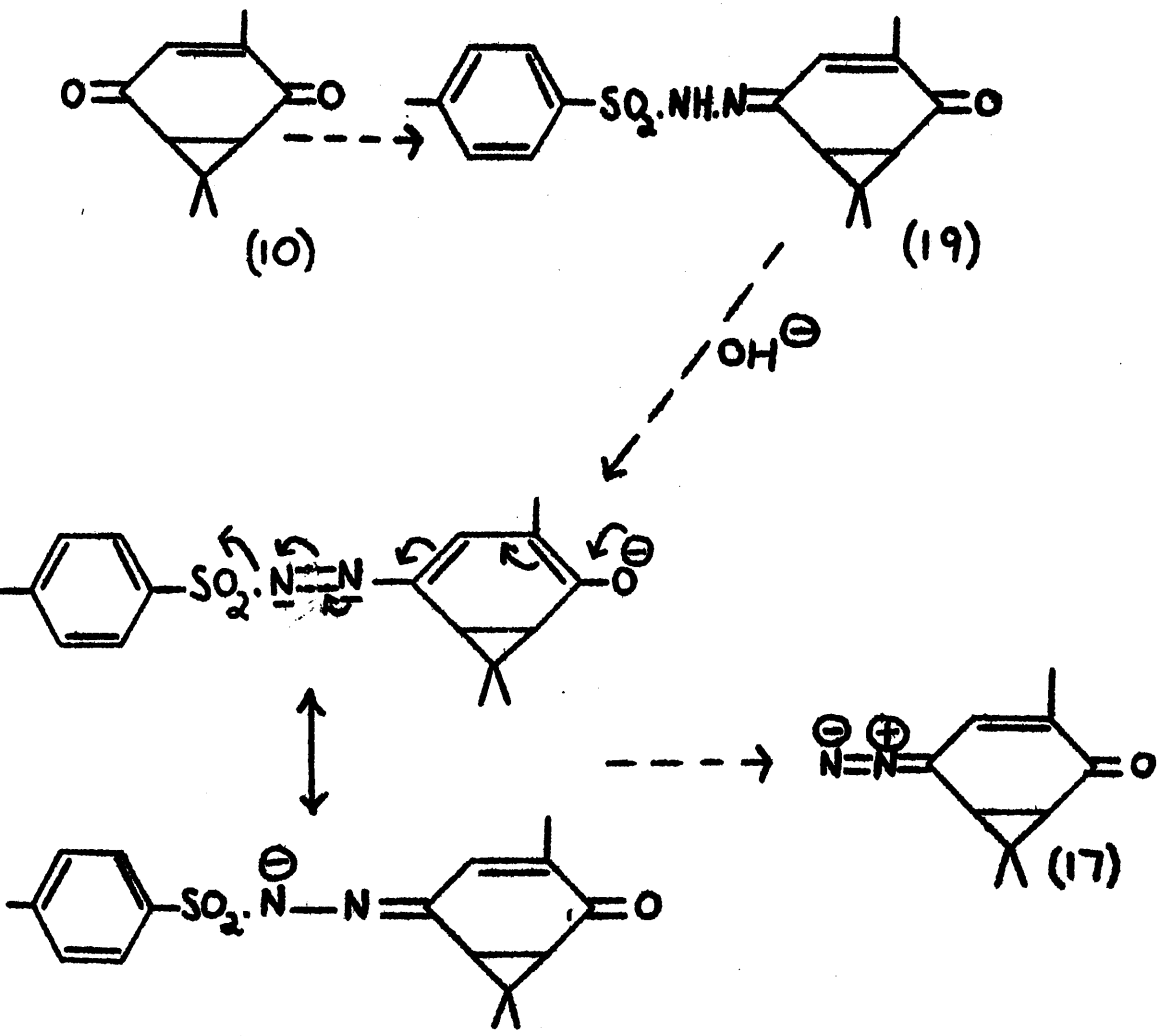
Treatment of oximino-eucarvone (13) in aqueous alkali with a mixture of sodium hypochlorite and ammonia (chloramine)[44, 45] led to the formation in poor yield, of a red liquid with a very strong band in the infra-red


Cl
HN
HON
O
(13)
OH
HN.N
H
O
HN=N
O
N≡N
O
(17)
N=N
O
Δ
:
O
[O]
O
O
(18)
(10)

at 2060 cm.$^{-1}$ Attempted distillation of this liquid under reduced pressure was accompanied by vigorous effervescence, and the appearance in the receiver of a yellow oil, which rapidly solidified. The solid thus obtained was recrystallized from light petrol and was identical (melting-point, mixture melting-point, and infra-red), with carenedione (10). Thermal decomposition of the red diazo-ketone (17) and generation of the carbene (18) was presumably followed by the attack of molecular oxygen at the bi-radical centre to give (10). The relative stability of the carbene (18) was shown by our failure to isolate any polymeric material from the distillation mixture, or indeed any product other than carenedione.

The method of Cava[43], which was a development of an earlier procedure employed by Bamford and Stevens[46], appeared to offer a milder route to the diazo-ketone (17). Unfortunately, we were unsuccessful in our attempts to prepare the requisite mono-toluenesulphonyl(tosyl) hydrazone of carenedione (19), since only the bis-tosylhydrazone was obtained, even with a deficiency of p-toluenesulphonyl hydrazine. Treatment of the bis-derivative with 1 equivalent of base, under the mild conditions employed by Cava, led to the recovery of starting-material.

Attempts have also been made to induce Beckmann rearrangements of oximino-eucarvone, utilizing such standard reagents as p-bromobenzenesulphonyl chloride in pyridine, and phosphorus pentachloride in ether.[47] Starting-material was recovered from these experiments, along with small


O
O
SO2.NH.N
O
(10)
(19)
OH⊖
SO2.N=N
O⊖
SO2.N⊖—N
O
⊖N=N⊕
O
(17)

amounts of carenedione formed by deoximation.

In our attempts to convert oximino-eucarvone to carenedione — a conversion best accomplished, as already described, by the use of nitrous acid — we made use of a number of well-known procedures. Treatment of the oximino-ketone with formaldehyde and dilute hydrochloric acid[48] at 100° led to extensive degradation of the molecule, but refluxing with laevulinic acid and hydrochloric acid[49] gave a small amount of a yellow, nitrogen-containing solid. Mass-spectroscopic and analytical examination of this compound pointed to the formula $C_{10}H_{11}O_2N$. The yield obtained by the above method was very poor, however, and a much better yield (38%) of the rearrangement product was obtained by stirring oximino-eucarvone at 100°, in a two-phase system of petrol (b.p. >120°) and 2N sulphuric acid. About 35% of starting-material was also recovered under these conditions, the remaining material being a deep blue amorphous solid, which was not investigated farther. The yield of the rearrangement product was not significantly affected by conducting the reaction under nitrogen, indicating that molecular oxygen was not involved. (The formula $C_{10}H_{11}O_2N$ for the rearrangement product involves the formal loss of two hydrogen atoms from oximino-eucarvone).

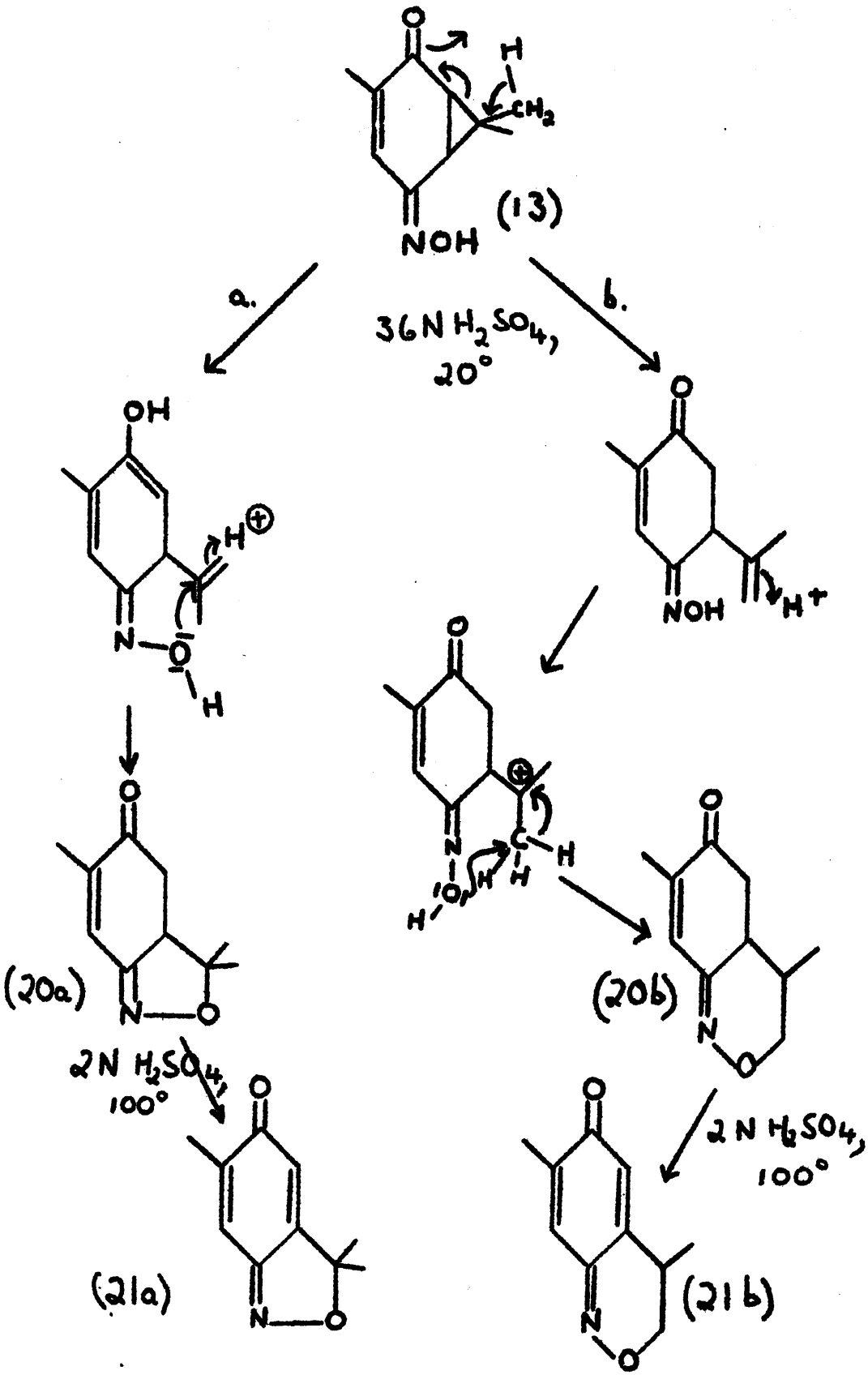
When oximino-eucarvone was dissolved in concentrated sulphuric acid at 20°, and allowed to stand for 4 hours, a pale yellow crystalline compound, isomeric with oximino-eucarvone, was isolated. This second rearrangement product was dissolved in very dilute alkali at 100°, through which

a stream of oxygen was passing,[50] and afforded, in good yield, a yellow solid identical (melting-point, mixture melting-point, and infra-red) with the first rearrangement product. Since this experiment establishes fairly accurately the relationship between the two rearrangement products, the experiments described in the following pages refer only to the initial, yellow rearrangement product.

Reduction of the rearrangement product with zinc in acetic acid rapidly discharged the yellow colour, which reappeared on leaving the mixture overnight exposed to the air. The ultra-violet absorption spectrum of the rearrangement product had λmax. 329 mμ (log ε,4.37), and the infra-red had $\nu_{max.}^{CCl_4}$ 1653, 1632 cm.$^{-1}$, indicating the presence of a highly conjugated, possibly quinonoid, carbonyl group.

When the reduction with zinc in acetic acid was carried out in the presence of acetic anhydride, a solid acetate was obtained. The infra-red of this material, $\nu_{max.}^{CCl_4}$ 1765, 1670 cm.$^{-1}$ was indicative of the presence of both a phenolic acetate and of an N-acetyl group. The solid-state infra-red spectrum confirmed the presence of an aromatic ring and, almost certainly, of a gem-dimethyl group. The ultra-violet spectrum had λmax. 268 mμ (log ε,4.17). Mass-spectrometric determination of the molecular weight of the reduction product led to the value 263, which was consistent with its formulation as a diacetate.

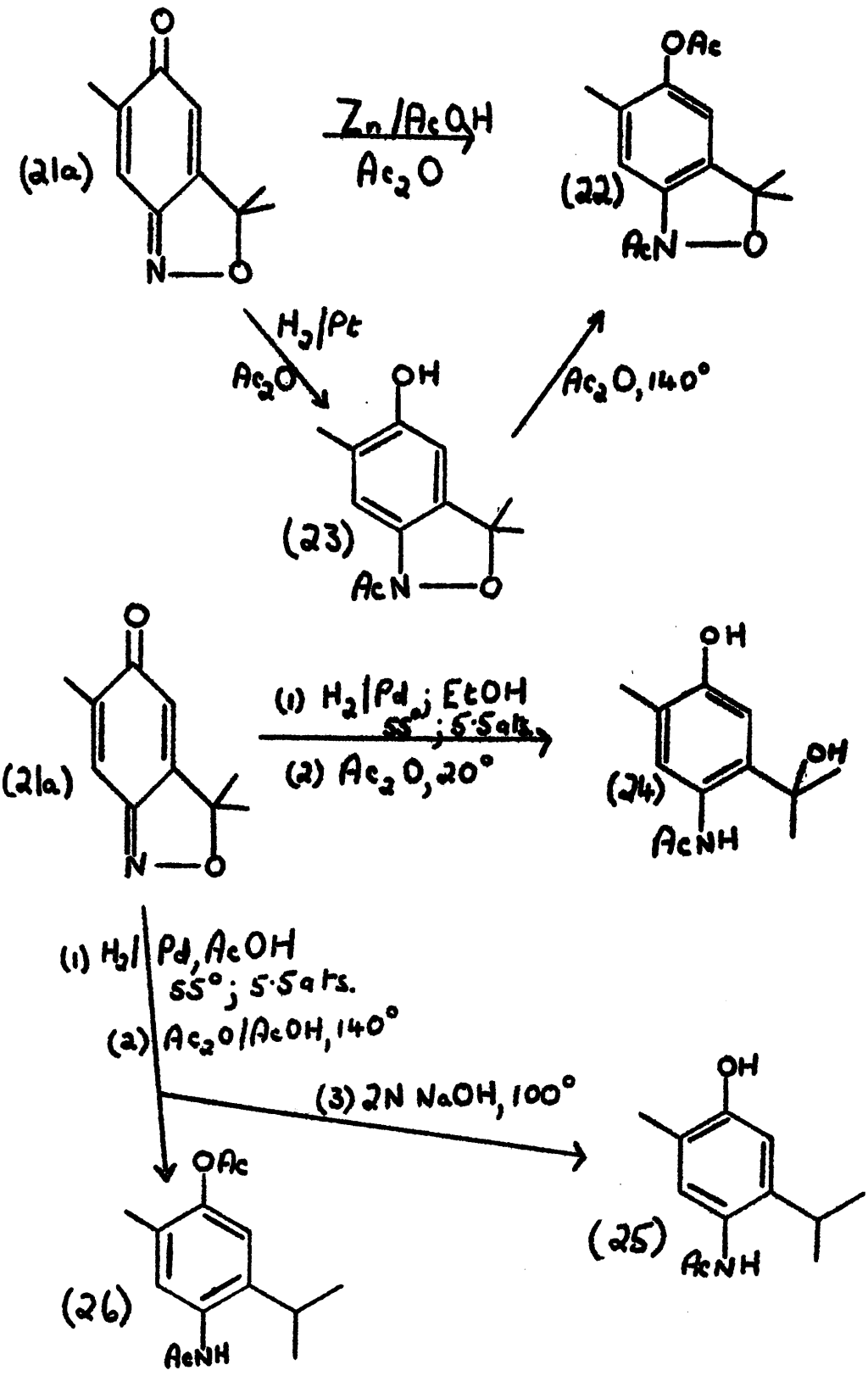
Catalytic hydrogenation of the rearrangement product over platinum in a mixture of acetic acid and acetic


(13)
NOH
a.
b.
36N H2SO4,
20°
OH
H⊕
N
O
H
NOH
H+
(20a)
(20b)
2N H2SO4,
100°
2N H2SO4,
100°
(21a)
(21b)

anhydride yielded a solid phenolic, N-acetyl derivative ($\nu_{max.}^{CCl_4}$ 3615, 1668 cm.$^{-1}$). This compound, on refluxing for a short while with acetic anhydride, gave a diacetate identical (melting-point, mixture melting-point, and infra-red) with the product of reduction with zinc.

As a result of these experiments, and the facile oxidation of the rearrangement product obtained from concentrated sulphuric acid, we were now in a position to postulate two probable formulae for the rearrangement products. A number of cases of iso-oxazoline formation by α/β-unsaturated ketoximes in concentrated sulphuric acid are known,[51,52] and the attack of the oxygen atom of the oxime group on the cyclopropane ring in (13) seems a logical extension of this reaction. Of the two formulae (20 a) and (20 b), the former seems more likely on mechanistic grounds. At 20°, the dihydro-quinonoid derivative appears to be reasonably stable, but in dilute sulphuric acid at 100°, dehydrogenation of (20) occurs with the formation of the fully quinonoid, yellow rearrangement product with structure (21 a) or (21 b). The same reaction occurs on treatment of (20) with oxygen in dilute alkali, this method being quite general for the oxidation of 1,4-diketones to the corresponding enediones[50].

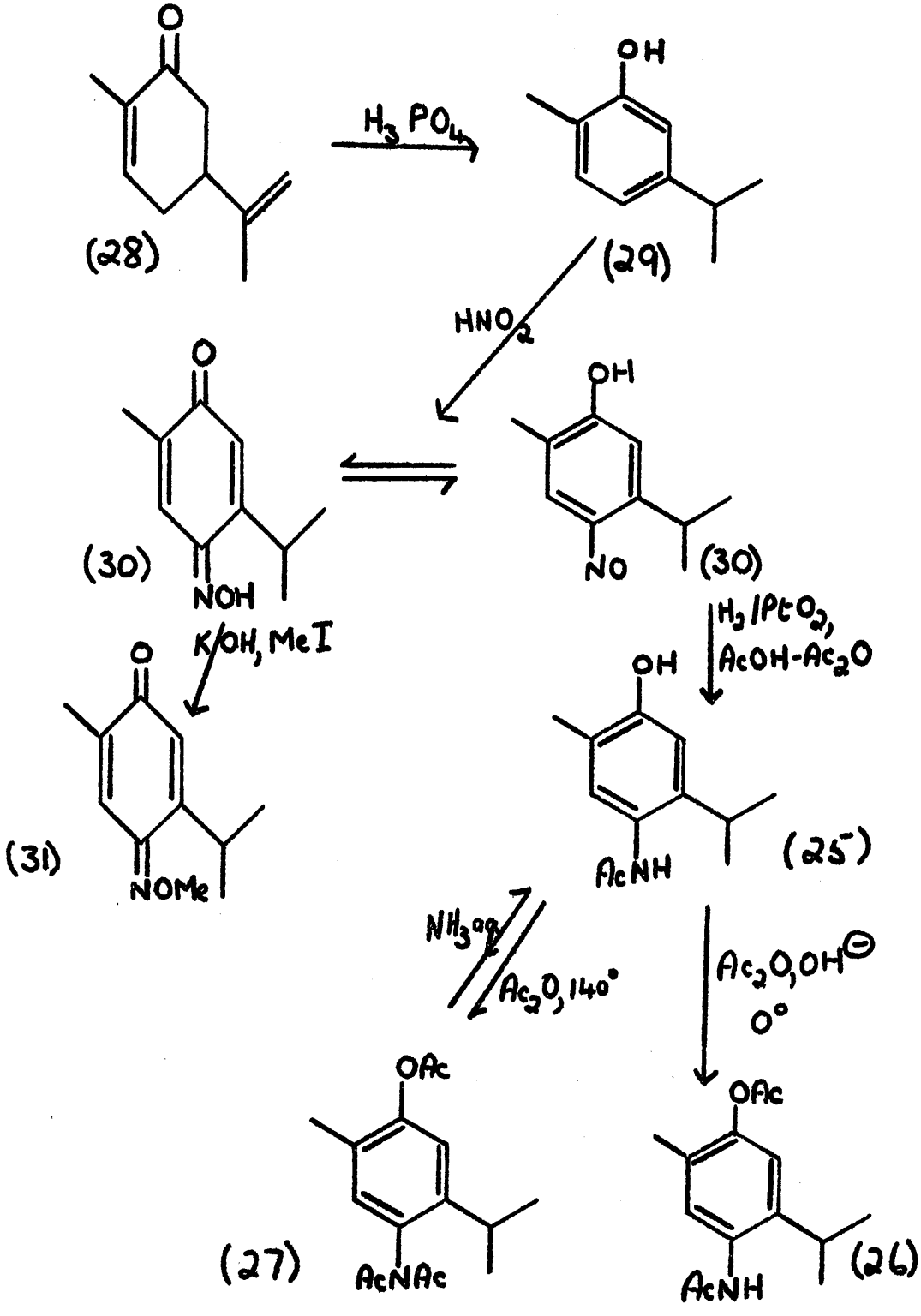
The structures of the products of zinc in acetic acid reduction, and of catalytic hydrogenation over platinum, seem to be represented best by (22) and (23) respectively. We are for the moment assuming that the heterocyclic ring present is an iso-oxazoline, rather than a 1,2-oxazine, system - evidence in favour of this assumption is described below.


(21a)
Zn/AcOH
Ac2O
(22)
OAc
AcN—O
H2/Pt
Ac2O
OH
Ac2O, 140°
(23)
AcN—O
(21a)
(1) H2/Pd; EtOH
55°; 5·5 atm.
(2) Ac2O, 20°
(24)
OH
OH
AcNH
(1) H2/Pd, AcOH
55°; 5·5 atm.
(2) Ac2O/AcOH, 140°
(3) 2N NaOH, 100°
(26)
OAc
AcNH
(25)
OH
AcNH

In order to establish with certainty the nature of the heterocyclic ring present in these rearrangement products, we carried out a number of hydrogenolytic experiments on compound (21). Only that compound with formula (21a) could reasonably be expected to yield a product derived by cleavage of the C-O bond in the heterocyclic ring, since this bond, unlike the corresponding bond in formula (21b), constitutes a benzylic ether group. Hydrogenolysis of the yellow, quinonoid rearrangement product in the presence of palladium-charcoal in ethanol, followed by treatment of the crude product with acetic anhydride at 20°, gave a hydroxy-compound of molecular weight 223. This compound had $\nu_{max}^{CCl_4}$ 3650,3570. λ_1 max. 252 mμ (log. ε , 4.11) ; λ_2 max. 285 mμ (infl.) (log ε ,3.51), and has been assigned the formula (24). It was not identical with either of the previously described reductive acetylation products, nor was it identical with 4-acetamino-carvacrol (25) or 4-acetamino-carvacryl acetate (26).

The hydrogenolysis was repeated, under the same conditions, but in acetic acid as solvent. Brief refluxing of the product with acetic anhydride gave a principal product identical (melting-point, mixture melting point, and infra-red) with authentic 4-acetamino-carvacryl acetate (26). The latter compound has not so far been described, but was readily obtained from 4-acetamino-carvacrol (25) by acetylation with acetic anhydride in sodium hydroxide at 0°.

Hydrolysis of a non-crystalline acetate derivative also obtained from the hydrogenolysis, led to the formation of a


O
H3PO4
OH
(28)
(29)
HNO2
O
OH
(30)
NOH
NO
(30)
K/OH, MeI
H2/PtO2,
AcOH-Ac2O
O
OH
(31)
NOMe
AcNH
(25)
NH3aq
Ac2O, 140°
Ac2O, OH⊖
0°
OAc
OAc
(27)
AcNAc
AcNH
(26)

crystalline N-acetyl derivative identical (melting-point, mixture melting-point, and infra-red) with 4-acetamino-carvacrol (25). This compound, like the others in the model series (Table 1), was prepared from carvone (28) by standard procedures.

A further interesting feature of this series of rearrangement products and their derivatives concerned the rather high intensity values associated with the ultra-violet absorption maxima of the compounds (22) and (23) compared with essentially similar compounds in the model series (Table 1). The so-called "ortho-effect"[53] must be considered to apply in the case of 4-acetamino-carvacrol (25), and its derivatives (26) and (27). In these compounds the ortho iso-propyl group causes the N-acetylamino group to be distorted out of the plane of the aromatic ring. The transfer of electron density from nitrogen to the aromatic ring is thus impaired, with a consequent marked reduction in the intensity of the main absorption band, relative to that observed for p-hydroxyacetanilide.

On the other hand, in our bicyclic reductive acetylation products (22) and (23) this steric effect is not observed, since the acetylamino group is virtually free of distortion, and there is free movement of electron density from the nitrogen lone-pair to the ring. An example of a similar skeletal structure is that of 1,2,3,4,10,11-hexahydro-6-methoxy-9-acetylcarbazole (32), a compound which was studied in relation to the structure of the alkaloid aspidospermine[54]. In our view, so marked is the division between the two categories of acetanilide derivatives compared in Table 2, that it was possible to

TABLE 1

Rearrangement series

Compound	λmax.	log.ε
(13)	295	4.00
(20a)	300	3.96
(21a)	329	4.37
(22)	268	4.17
(23)	269	4.19
(24)	252	4.11

Model series

Compound	λmax.	log.ε
(30)	305	4.32
(31)	320	4.30
(26)	274	3.01
(25)	280	3.35
(27)	266) 274)	2.96) 2.93)

TABLE 2

p-substituted Acetanilide derivs. with "normal" ε values

Substituent	λmax.	log.ε
$-CH_3$	245	4.17[53]
$-C(CH_3)_3$	245	4.20[53]
-OH	250	4.27[57]
-OMe	250	4.20[56]
-OAc	247	4.13[57]
(32)	261	4.16[54]

o-substituted Acetanilide derivs. with "abnormal" ε values

Substituent	λmax.	log.ε
$-CH_3$	230	3.80[53]
$-C(CH_3)_3$	230	3.50[53]
(25)	280	3.35
(26)	274	3.01

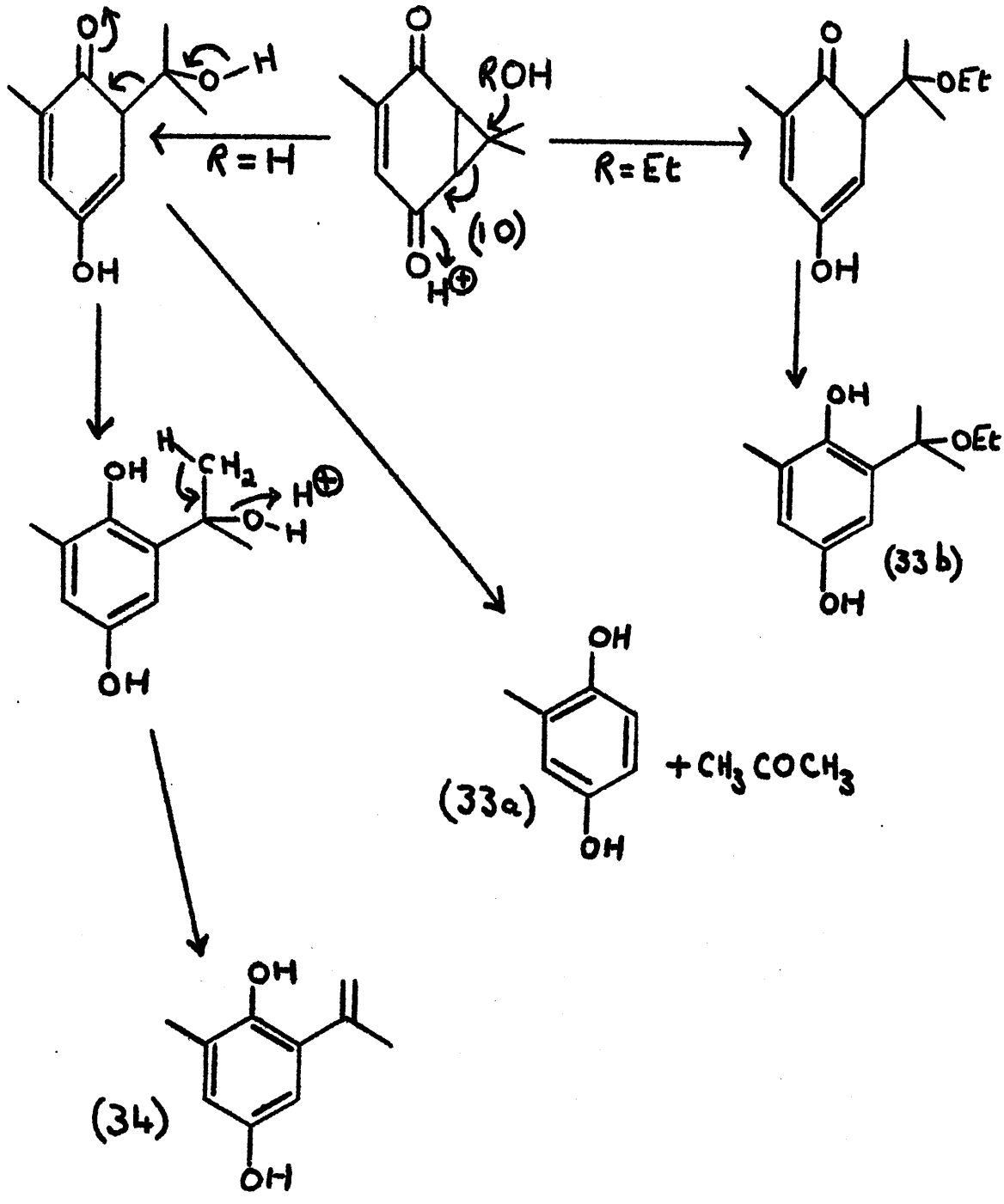
classify the various reduction products which we obtained as monocyclic or bicyclic, merely from a consideration of their ultra-violet absorption spectra.

The results of the degradative procedures described, in conjunction with an examination of the ultra-violet spectra and other physical measurements, have led us to propose the structures (20a) and (21a) for the rearrangement products of oximino-eucarvone.

Other aspects of the chemistry of the bicyclic ketone, carenedione (10), and more particularly the effect of acid, and of ultra-violet light, are now considered briefly.

Treatment of carenedione with a refluxing ethanolic solution of sulphuric acid gave rise to a high-boiling, reddish liquid, which exhibited hydroxyl and aromatic bands (3400, 1620, 1510 $cm.^{-1}$) in the infra-red, and possessed an ultra-violet spectrum characteristic of known hydroquinone derivatives (225, 292 $m\mu$). When the ultra-violet spectrum was repeated in the presence of potassium hydroxide, a bathochromic shift (238, 307 $m\mu$) was observed, similar to those observed in the formation of the monovalent anions of several known hydroquinones.[55] The rearrangement product was soluble in 4N sodium hydroxide, and afforded a crystalline derivative with chloroacetic acid.

In view of the above results, and our inability to obtain a colourless sample of the material, indicating its ease of oxidation, we are of the opinion that our rearrangement product is a hydroquinone derivative. The three most likely structures for the product, on mechanistic grounds, are (33a), (33b), or (34). The


R = H
R = Et
ROH
(10)
OEt
(33b)
(33a)
+ CH3COCH3
(34)
OH

mechanisms involved are illustrated on the accompanying flowsheet. Structure (34) was rejected on the ground that no evidence for a styrene type of structure was obtained on examination of the ultra-violet absorption spectrum.

Nuclear magnetic resonance examination of the rearrangement product indicated that the product might well be a constant-boiling mixture of (33a) and (33b). While there was evidence for a $-CH_2\ CH_3$ group in the form of a triplet (τ values around 8.7), the weight of aromatic protons ($\tau = 3.2$) in relation to $C - CH_3$ protons seemed to be more akin to a structure such as (33a).

This possibility was farther enhanced by an examination of the products of oxidation of the rearrangement product with chromium trioxide in acetone. From one experiment, a mono-2:4-dinitrophenylhydrazone was obtained, which, on the basis of the analytical and ultra-violet absorption data, was the compound (36). From a second experiment, on a rather larger scale, a quinone was obtained, corresponding to toluquinone (37).

In our discussion, products arising from the alternative method of opening the cyclopropane ring in carenedione appear to have been neglected. Apart from the mechanistic consideration that the carbonyl group which is in hyperconjugation with the allylic C-methyl group in carenedione is likely to be protonated preferentially, we have succeeded in isolating as solid derivatives only the 2:4-dinitrophenylhydrazone mentioned above, and an aryloxy-acetic acid, with one carboxyl group. This indicates that the second -OH group in the hydroquinone is so sterically

hindered as to be crypto-phenolic.

Further evidence on this point was provided by the formation of a liquid acetate. Treatment of the rearrangement product with acetic anhydride, in the presence of zinc and acetic acid to prevent autoxidation, gave a liquid, which analysed for a mono-acetyl derivative, although the analytical data were not consistent with (35a) or (35b). This acetate still exhibited an infra-red band at 3500 $cm.^{-1}$ although this was of relatively lower intensity, but it did not dissolve in 4N sodium hydroxide.

On the basis of the evidence available, we are unable to assign a structure to the acid rearrangement product, and lack of time has prevented a fuller investigation.

The irradiation of carenedione with a mercury lamp in ethanolic solution has afforded a liquid, which appears from the infra-red spectrum to be an ester (1760, 1720 $cm.^{-1}$). The ester shows no ultra-violet absorption above 210 $m\mu$.

Since it was suspected that the above product might be an ethyl ester, arising from the attack of solvent on a ketene intermediate, the irradiation was repeated using aqueous dioxan, in an attempt to isolate a crystalline acid. The chief product, however, obtained by chromatography was a very viscous liquid. This compound analyzed fairly satisfactorily for the addition of one molecule of water to the molecular formula of carenedione, but it did not appear to be acidic, nor did it show any reaction with diazo-methane. The material exhibited infra-red absorption indicative of a hydroxy-lactone, or a lactol (3500, 1770 $cm.^{-1}$), but none of the usual hydroxy-

derivatives was obtained, and the hydroxyl band was still present after treatment with excess chromium trioxide in acetone.

The extremely viscous nature of this product in relation to the expected molecular weight, indicates that it may be a mixture of two or more compounds.

EXPERIMENTAL

Oxidation of eucarvone to carenolone (9) with selenium dioxide - Eucarvone (10.0 g., 0.069 m.) was stirred with selenium dioxide (2.50 g., 0.068 m.) in refluxing ethanol (50 ml.), for a period of 20 hours. The red solution was cooled, filtered through 'Celite', and shaken with mercury overnight. The solution was again filtered, evaporated to small bulk, and poured into a large volume of water. Extraction with ether, washing (water), and drying (magnesium sulphate) gave, on evaporation, a dark red oil. This oil was flash-distilled, and the distillate collected over the range 40-120°/0.15 mm. This crude product (5.6 g.) was then fractionally distilled. The distillate collected between 54-78°/0.35 mm., n_D^{20} 1.5085, was shown by infra-red examination to consist of unreacted eucarvone (3.5 g., 35%). The remaining liquid had b.p. 78-110°/0.35 mm. n_D^{20} 1.5160. Addition of light petrol (b.p. 40-60°) to this material produced a crop of white crystals (0.25 g., 2.5%) on cooling to -10°. Recrystallization from petrol afforded carenolone, m.p. 85° (white needles). $\nu_{max.}^{Nujol}$ 3410, 1643, 1625, 990 cm.$^{-1}$ $\nu_{max.}^{CHCl_3}$ 1658, 1643 cm.$^{-1}$

Oxidation of carenolone (9) to carenedione (10) - Carenolone (200 mg.) was dissolved in carbon tetrachloride (15 ml.) and shaken with manganese dioxide (1.2 g.) at 20° for 48 hours. The product obtained by filtration and evaporation was carenedione (183 mg., 92%), m.p. 90-91°, pale yellow needles from petrol (b.p. 60-80°). $\nu_{max.}^{Nujol}$ 1645, 1610, 1000 cm.$^{-1}$ $\nu_{max.}^{CHCl_3}$ 1658, 1620 cm.$^{-1}$

Preparation of oximino-eucarvone (13) - Sodium (0.7 g., 0.031 m.) was dissolved in ethanol (30 ml.), and the resulting solution cooled to 0° before adding butyl nitrite (3.1 g., 0.030m.). Eucarvone (4.5 g., 0.030 m.) was then added slowly, with stirring at 0°. After the addition of the ketone (15 mins.), the violet-coloured reaction mixture was allowed to stand at 20° for 48 hours. The solution was then evaporated under reduced pressure to small volume, diluted with water (50 ml.), and extracted with ether. The aqueous phase was cooled to 5° and acidified to pH 4-5. Extraction with ether, followed by washing (brine) until neutral, gave on drying and evaporation a coffee-coloured, semi-solid mass. This material was dissolved in the minimum amount of warm methylene chloride. Addition of n-pentane yielded pale brown crystals of the desired oxime (3.3 g., 61%), m.p. 155-156°. A colourless sample of the same melting-point was obtained by sublimation. νmax. 3410, 1643, 1600, 1020, 1000 cm.$^{-1}$ λmax. 224 mμ (logε, 4.01); 295 mμ (log ε, 4.08).

Conversion of oximino-eucarvone (13) to carenedione (10) - Oximino-eucarvone (1.06 g.) was dissolved in acetic acid (12 ml.), to which sodium nitrite (4.8 g.) in water (10 ml.) was added slowly, with shaking. After standing for 4 hours with occasional shaking, the initially-formed deep red colour had disappeared and the effervescence had ceased. The reaction mixture was poured into a large volume of aqueous sodium acetate, and extracted with benzene in the usual way. The crude yellow solid obtained on evaporation had m.p. 60-70°. This solid was dissolved in benzene, and eluted from Grade III neutral alumina with 10% ether in

benzene. Evaporation of the eluate gave carenedione (0.75 g., 71%), m.p. 89-90°, undepressed on admixture with an authentic sample prepared by the previously described oxidative procedures. (For larger scale work, it was found that mechanical stirring was necessary to obtain yields comparable with the above).

Attempted oxidation of carenedione (10) with lead tetraäcetate - Carenedione (0.20 g.) was refluxed for 24 hours in benzene, under nitrogen, with excess freshly prepared lead tetraäcetate. At the end of this time, the mixture no longer turned moist starch-potassium iodide paper blue. The solution was filtered, washed (sodium hydrogen carbonate, water), and dried. Chromatography of the crude product on silica gel gave only starting-material (75%).

Attempted oxidation of eucarvone trityl enol-ether (14) with lead tetraäcetate - The enol-ether (0.58 g.) was treated as described in the previous experiment for 45 hours. Isolation and chromatography on silica gave only starting-material (0.41 g., 75%), and some triphenyl carbinol (30 mg., 5%), m.p. 163°, identified by its infra-red spectrum.

Attempted oxidation of carenedione (10) with tert-butyl perbenzoate - Carenedione (0.28 g., 0.002 m.) was mixed with tert-butyl perbenzoate (0.35 g., 0.002 m.) and a trace of cuprous bromide, and heated at 110-112° for 2 hours. On cooling, the product was dissolved in ether, washed (2N sodium carbonate, water) and dried. Chromatography on silica yielded only unchanged carenedione.

Attempted oxidation of eucarvone trityl enol-ether (14) with tert-butyl perbenzoate - The enol-ether (0.31 g., 0.001 m.) was dissolved in dry methanol (2 ml.) containing cuprous bromide (32 mg.). Tert-butyl perbenzoate (0.19 g., 0.001 m.) was added over a period of 1 hour at 110-112°, under nitrogen. After 3 hours, the product was worked-up as described in the previous experiment, but the solid so obtained was identical (infra-red) with starting-material.

Reaction of carenedione (10) with N-bromosuccinimide - Carenedione (0.33 g., 0.002 m.) was dissolved in 'Analar' carbon tetrachloride (10 ml.), to which N-bromo-succinimide (0.38 g., 0.002 m.) and benzoyl peroxide (20 mg.) were added. Irradiation for 18 hours with a 40 watt Tungsten lamp was necessary to initiate the reaction, which was then completed by refluxing for a further 3 hours. The solution was then chilled, filtered to remove succinimide, and carefully evaporated at 20°. The yellow oil so obtained was taken up in acetic anhydride (5 ml.) and heated with excess fused potassium acetate at 90° for 1 hour, under nitrogen. The mixture was poured on to crushed ice and extracted with benzene. The usual processing gave a dark brown oil, νmax. 1745 cm.$^{-1}$ The infra-red spectrum also revealed the presence of a mixture, which was not separated on silica, and decomposed very rapidly on alumina. Treatment with excess 2:4-dinitrophenylhydrazine gave no crystalline derivative, even after chromatography on Kieselguhr-Bentonite.

Eucarvone trityl enol-ether (14) - Eucarvone, (1.33 g., 0.0089 m.) in dry dioxan (10 ml.) was added to a refluxing

solution of freshly prepared sodamide[58] (0.56 g., 0.014 m.) in dioxan (40 ml.), under nitrogen. Evolution of ammonia had ceased after 2 hours, and the solution of the sodio-salt was cooled to 20° before adding triphenylmethyl (trityl) chloride (3.82g., 0.014 m.) in benzene (10 ml.) with stirring, during 45 mins. The mixture was refluxed for 1 hour, then stirred overnight at 20° before pouring into a large volume of water, and extracting with benzene. On evaporation to small bulk (5 ml.) and adding pentane, the enol-ether (2.20 g., 62%) was obtained as a pale brown solid. Recrystallization from iso-propanol afforded beautiful white prisms, m.p. 186-189°. (litt. m.p., 196-200°)[42] λmax. 229 mμ (log ε,4.24). (Found: C,88.41; H,6.85. $C_{29}H_{28}O$ requires C, 88.73; H,7.19%).

Reaction of eucarvone trityl enol-ether (14) with N-bromosuccinimide - The enol-ether (0.39 g., 0.001 m.) was dissolved in 'Analar' carbon tetrachloride (10 ml.) and refluxed for 40 mins. with N-bromosuccinimide (0.18 g., 0.001 m.) and benzoyl peroxide (12 mg.). The red solution was chilled, filtered, and evaporated carefully at 20°. The yellow viscous product was then dissolved in acetic anhydride (10 ml.) and heated with excess fused potassium acetate at 70° for 1½ hours. The mixture was poured on to crushed ice, and extracted with benzene in the usual way. Evaporation gave a semi-solid product, which was then chromatographed on silica. The sole product isolated was a white solid, m.p. 67° (pentane), in less than 5% yield. There was a 75% recovery of starting-material. The unknown solid had λmax. 224 mμ (log ε,4.39); 255 mμ (log ε,4.02) (Found: C, 67.53; H,5.33. $C_{33}H_{31}O_5Br$ (16)

requires C, 67.47; H, 5.28%). The compound had strong acetate absorption, (1745 cm.$^{-1}$) in the infra-red, and gave a positive test for bromine. Mass-spectrometric measurements indicated a molecular weight in the region of 600. ($C_{33}H_{31}O_5Br$ requires M.W. 587).

Attempted oxidation of eucarvone trityl enol-ether (14) with mercuric acetate - The enol-ether (0.53 g., 0.0013 m.) was refluxed with stirring under nitrogen for 2 hours with a solution of red mercuric oxide (0.58 g., 0.0025 m.) in glacial acetic acid (15 ml.). The solution became quite dark, and this was accompanied by the formation of metallic mercury. The reaction mixture was cooled, poured into ice-water, and extracted with benzene. Chromatography of the crude product (0.52 g.) on silica led to a 75% recovery of unchanged enol-ether, along with triphenyl carbinol (15%), identified by its infra-red spectrum.

Oxidation of eucarvone trityl enol-ether (14) with selenium dioxide - The enol-ether (0.49 g., 0.0012 m.) was refluxed under nitrogen with selenium dioxide (0.33g., 0.003 m.) in acetic anhydride (1 ml.) containing a little water. After cooling, the reaction mixture was poured on to ice and extracted with ether. Chromatography of the crude product on silica afforded triphenyl carbinol (60%), and small amounts of starting-material.

Conversion of oximino-eucarvone (13) into diazo-carenone (17)- Oximino-eucarvone (3.58 g., 0.02 m.) was finely ground, and dissolved in 33% sodium hydroxide solution (6 ml.). The solution was diluted with water to 200 ml. and cooled to 0°.

Ammonia solution (S.G. 0.880; 10 ml.) was added with stirring, followed by dropwise addition of 2.7% sodium hypochlorite solution (220 ml.) over 1 hour. After stirring for a further 30 mins. at 0°, the aqueous solution was extracted with light petrol (b.p. 40-60°) for 2-, 2-, and 12-hour periods, using a suitable stirrer. The combined extracts were washed (water) and dried, before evaporating carefully at 30°. The crude product was a red liquid, νmax. 2060 cm.$^{-1}$, which distilled under reduced pressure (b.p. 60-90°/0.2 mm.) to a yellow semi-solid. Recrystallization from petrol (b.p. 60-80°) gave yellow prisms, m.p. 90-91°, undepressed on admixture with authentic carenedione. An attempt to isolate the pure diazo-ketone by chromatography on neutral alumina was no more successful.

Preparation and attempted decomposition of the p-toluenesulphonyl (tosyl) hydrazone of oximino-eucarvone (13). - The tosylhydrazone was prepared by mixing equivalent amounts of the compound and the reagent in methanol, warming briefly at 100° and setting aside for several hours. Recrystallization from ethanol gave white prisms, m.p. 182-183° (dec.) (Found: C, 58.21; H, 6.14; N,12.40. $C_{17}H_{21}O_3N_3S$ requires C,58.78; H,6.09; N,12.10%). λmax. 295 mμ (log ε,4.43).

The derivative (105 mg., 0.30 mmole) was dissolved in 0.1N sodium hydroxide solution (6.3 ml., 0.63 mmole) and stirred with methylene chloride under nitrogen. After 48 hours, the still colourless methylene chloride layer was separated and evaporated. No significant amounts of material were obtained. Acidification of the yellow aqueous

layer gave a virtually quantitative recovery of starting-material.

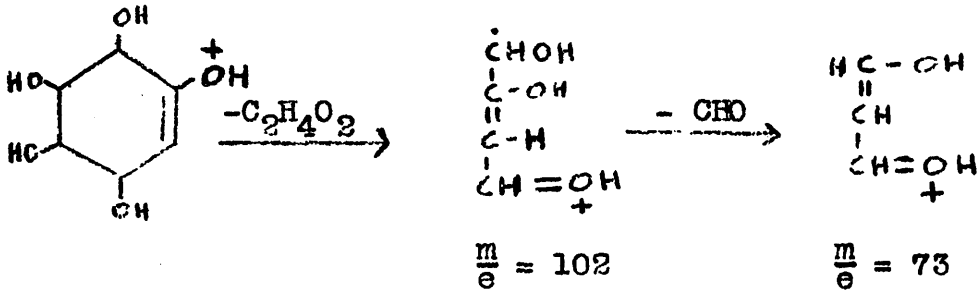
Preparation and attempted decomposition of the bis-tosylhydrazone of carenedione (10) - Attempted preparation of the mono-tosylhydrazone by treatment of carenedione with less than 1 equivalent of the reagent, under the conditions already described in the previous experiment, led only to the formation of the bis-derivative, m.p. 195° (dec.) - insoluble in all common solvents and mixtures of solvents. (Found: C,57.61; H, 6.03; N, 10.59. $C_{24}H_{28}O_4N_4S_2$ requires C,57.59; H,5.64; N,11.20%). λmax. 310 mμ (log ε,4.39).

Treatment of this compound with one equivalent of base, in the presence of methylene chloride yielded nothing but starting-material.

Attempted Beckmann rearrangements of oximino-eucarvone (13) - (a) - p-Bromobenzenesulphonyl chloride (6.5 g., 0.025 m.) was dissolved in dry pyridine (12 ml.), and the solution cooled to 0°. A solution of oximino-eucarvone (3.6 g., 0.02 m.) in pyridine (9 ml.) was then added slowly, with stirring. A red solution was produced from which pyridine hydrochloride rapidly crystallized. After allowing the solution to warm up to 20°, the mixture was stirred at 100° for 15 mins., before cooling and pouring into a mixture of ice and dilute sulphuric acid. After removal of some dark brown polymeric material by filtration, the aqueous solution was extracted with benzene in the usual fashion. The crude product was a semi-solid material which afforded only oximino-eucarvone and some carenedione by chromatography on Grade III neutral alumina.

(b) Oximino-eucarvone (1.193 g., 0.0067 m.) was suspended in ether and treated with excess phosphorous pentachloride at 10°, with frequent shaking. After 1½ hours, the dark-brown ethereal solution was poured on to ice and the ether layer removed. The usual processing gave a very dark viscous oil, which yielded no pure material after careful chromatography on alumina.

Attempted conversions of oximino-eucarvone (13) into carenedione (10) - (a) Oximino-eucarvone (2.5 g.) was refluxed in an aqueous solution containing formalin (20 ml.) and 2N hydrochloric acid (6 ml.). After 2 hours, the solution was cooled and extracted with methylene chloride. Washing, drying and evaporation yielded a dark brown oil, from which no crystalline material could be isolated.
(b) The oximino-ketone (1.6 g.) was heated at 100° for 2½ hours in a solution of laevulinic acid (9 parts by vol.) and N hydrochloric acid (1 part by vol.). After dilution with water, the product was extracted with methylene chloride in the usual way. The dark brown oil obtained on evaporation was re-extracted with benzene, refluxed briefly with charcoal, filtered, evaporated and extracted with hot petrol (b.p. 60-80°). The small amount of crystalline material obtained on cooling had m.p. 152-153°, after two recrystallizations (yellow needles). $\nu_{max.}^{KCl}$ 3045, 1655, 1610, 1585, 1515, 1375, 1365 cm.$^{-1}$ $\nu_{max.}^{CCl_4}$ 1653, 1632 cm.$^{-1}$ $\lambda_{max.}$ 329 mμ (log ε, 4.37). (Found: C, 67.42; H, 6.01; N, 7.99. $C_{10}H_{11}O_2N$ requires C, 67.78; H, 6.26; N, 7.91%). Molecular weight 177 (mass-spectrometer), in agreement with formula $C_{10}H_{11}O_2N$ (21a).



$\frac{m}{e}$ = 102 $\frac{m}{e}$ = 73

It is not yet possible to determine whether either or both of these mechanisms are valid.

The other fragment ions at lower mass numbers can be obtained by a variety of routes. As an instance, the ion of $\frac{m}{e}$ = 60 can be obtained in six ways by removal of $C_2H_4O_2$ fragments from the molecular ion.

It can thus be seen, from the evidence afforded by the few examples quoted here that some information about the structure of small polyhydroxy compounds can be derived from their mass spectra at higher mass numbers. At lower mass numbers there is a greater possibility that several processes will give rise to ions of the same mass. The use of the continuous volatilisation method appears to be quite adequate to deal with such involatile compounds. Ion-molecule reactions provide a method for accurate molecular weight determination.

formula $C_{10}H_{13}O_2N$ (20a).

Oxidation of second (dihydro-) rearrangement product (20a) - The dihydro-compound (20a) (95 mg.) was dissolved in ethanol (60 ml.) containing potassium hydroxide (200 mg.). A moderately fast stream of oxygen was bubbled through the solution, which was refluxed for 1½ hours. The initially pale pink solution became finally a deep red colour. Most of the ethanol was removed under reduced pressure, before pouring the residual solution into water and making just acid with dilute hydrochloric acid. Extraction with ether gave on evaporation a brown solid. Chromatography on Grade I neutral alumina and elution with benzene afforded a yellow solid (46 mg., 50%). Recrystallization from petrol (b.p. 60-80°) gave yellow needles, m.p. 152-153°. M.p. 150-153°, on admixture with the initial yellow rearrangement product (21a). The infra-red spectra of the two solids were identical.

Reductive acetylation of the quinonoid rearrangement product (21a) - (a) Compound (21a) (41 mg.) was refluxed with zinc dust (100 mg.) in a 1:1 mixture of acetic acid - acetic anhydride (3 ml.). The white solid (36 mg.) isolated by pouring the reaction mixture on to crushed ice, was recrystallized from petrol (b.p. 60-80°), m.p. 135-136°. $\nu_{max.}^{KCl}$ 1775, 1765, 1655, 1620, 1500, 1375, 1360, 1205 cm.$^{-1}$ $\nu_{max.}^{CCl_4}$ 1765, 1670 cm.$^{-1}$ $\lambda_{max.}$ 268 mμ (log ε, 4.17). (Found: C, 63.89; H, 5.94; N, 5.46. $C_{14}H_{17}O_4N$ requires C, 63.86; H, 6.51; N, 5.32%). Molecular weight (mass-spectrometer) 263±1. (b) Compound (21a) (156 mg.) was hydrogenated over platinum oxide (98 mg.) in a 1:1 mixture of acetic acid - acetic anhydride (10 ml.). After one hour the absorption of

hydrogen (45 ml., 1.2d.b. equivalents) had ceased, and the yellow solution had become quite colourless. After filtering off the catalyst, the bulk of the solvent was removed under reduced pressure, and crushed ice added to the remaining solution. The white solid (140 mg.) which separated was collected, dried, and recrystallized from 30% ethanol as white plates, m.p. 193-194°. The solid could also be purified by sublimation. $\nu_{max.}^{KCl}$ 3110, 1615, 1505, 842, 792 cm.$^{-1}$ $\nu_{max.}^{CCl_4}$ 3615, 1668 cm.$^{-1}$ $\lambda_{max.}$ 269 mμ (log ε, 4.19). (Found: C, 65.25; H, 6.59; N, 6.58. $C_{12}H_{15}O_3N$ requires C, 65.14; H, 6.83; N, 6.33%).

The above product was soluble in cold 4N sodium hydroxide solution, with the production of a deep red colour. Acidification of this solution with hydrochloric acid produced a bluish colour, and a brown solid, not farther investigated.

Refluxing with acetic anhydride for 30 minutes gave, on pouring into water, a white solid, m.p. 135°, undepressed on admixture with the product of method (a). The infra-red spectra of the two solids were super-imposable.

Hydrogenolysis of the quinonoid rearrangement product (21a) - (a) The quinonoid compound (21a) (690 mg.) was dissolved in ethanol (75 ml.). 10% palladium-charcoal (300 mg.) was added, and the mixture saturated with hydrogen in a thick-walled bottle to a pressure of 5.05 atmospheres. After shaking for 30 mins. at 20°, the pressure had fallen to a constant value of 4.60 atmospheres. The hydrogenation mixture was then heated to 55° at a pressure of 5.55 atmospheres for 20 hours. After cooling and releasing the excess hydrogen, the now colourless solution was filtered, and

evaporated to small volume. During this process some darkening of the solution occurred, and the product obtained by pouring the solution into water and extracting with benzene was a deep purple solid. The yield of this material was not good (160 mg.), but this is perhaps not surprising in view of the fact that the expected product is a free p-aminophenol. Treatment of the purple-coloured product with acetic anhydride at 20°, afforded a highly water-soluble white solid. This compound was isolated by adding benzene, filtration, and thorough washing of the product with more benzene to remove the excess acetic anhydride. Recrystallization from ethyl acetate-petrol (3:1) gave white prisms, m.p. 178-179°, mixed with 4-acetamino-carvacrol, m.p. 150-170°. $\nu_{max.}^{KCl}$ 3240, 1640, 1550, 888, 820 cm.$^{-1}$ $\nu_{max.}^{CCl_4}$ 3650, 3570 cm.$^{-1}$ $\lambda_{max.}$ 252 mμ (log ε,4.11); 285 mμ (log ε,3.51). (Found: C,64.48; H,7.67; N, 6.21. $C_{12}H_{17}O_3N$ requires C, 64.55; H,7.68; N, 6.27%). Molecular weight (mass-spectrometer) 223, in agreement with the formula $C_{12}H_{17}O_3N$ (24). Further amounts (300 mg.) of this compound were obtained by prolonged ether extraction of the original aqueous mother liquors, and treatment with acetic anhydride as already described.

An attempt to remove the benzylic -OH in (24) with boiling acetic anhydride, followed by catalytic hydrogenation, yielded no crystalline material.

(b) The hydrogenolysis of the quinonoid compound (21a) (730 mg.) was carried out as described in (b), using acetic acid as solvent. As soon as the pressure bottle was opened, excess acetic anhydride was added to prevent autoxidation of the product, by prior acetylation. After filtration, the reaction mixture was distilled to small volume under nitrogen

and the residual solvent evaporated under reduced pressure. The crude product was dissolved in a mixture of ethanol-ethyl acetate, and filtered through a pad of silica gel-'Celite'. Evaporation afforded an almost colourless oil, which was dissolved in hot petrol (b.p. 60-80°). Crystals appeared on cooling and scratching. Recrystallization from petrol-ethyl acetate (2:1) gave fine white needles, m.p. 161°, undepressed on admixture with authentic 4-acetamino-carvacryl acetate (26). νmax. 3200, 1745, 1640, 1535, 1495, 1240 cm.$^{-1}$ (identical with 4-acetamino-carvacryl acetate). λmax. 274 mμ (logε, 2.99). (Found: C, 67.22; H,7.56; N, 5.49. $C_{14}H_{19}O_3N$ requires C, 67.44; H, 7.68; N, 5.62%).

The solid compound so obtained was, however, in minor amount. Evaporation of the petrol mother liquors yielded a viscous gum (350 mg.), b.p. 90-100°/0.5 mm. νmax. 1760, 1705, 1650, 1500, 930, 845, 800 cm.$^{-1}$ λmax. 265, 274 mμ.

This gum was refluxed in 2N sodium hydroxide for 20 mins. before cooling, extracting with ether, acidifying the aqueous layer, and re-extracting. The usual processing of the latter ether extracts gave on evaporation a white solid, m.p. 179-180°, from ethyl acetate-petrol. M.p. 177-179°, on admixture with authentic 4-acetamino-carvacrol (25). νmax. 3220, 1635, 1620, 1540, 1510, 1205, 880, 862 cm.$^{-1}$ (Identical with infra-red of 4-acetamino-carvacrol). λmax. 280 mμ (log ε, 3.30). (Found: C, 69.47; H,8.11; N, 7.29. $C_{12}H_{17}O_2N$ requires C, 69.54; H,8.27; N, 6.76%).

Preparation of p-nitrosocarvacrol (thymoquinone monoxime) (30) - Carvacrol (29), conveniently prepared by the isomerization of carvone (28) with phosphoric acid, was converted to

p-nitrosocarvacrol by the procedure of Kremers et al.[59] used in the preparation of p-nitrosothymol. Yield of recrystallized product (53%) as golden prisms from benzene, m.p. 156°. λmax. 305 mμ (log ε, 4.32).

Preparation of thymoquinone monoxime O-methyl ether (31) - p-Nitrosocarvacrol (1.2 g.) was dissolved in 10% methanolic potassium hydroxide solution (20 ml.), and refluxed with methyl iodide (4.5 g.) for 1 hour. On pouring on to crushed ice, the product was obtained as a golden brown solid (0.5 g., 40%). Recrystallization from pentane at -20° gave yellow prisms, m.p. 38-39°. λmax. 320 mμ (logε, 4.30).

4-Acetamino-carvacrol (25) - p-Nitrosocarvacrol (30) (820 mg.) was catalytically reduced over platinum oxide (520 mg.), in a 1:1 mixture of acetic acid-acetic anhydride (20 ml.). After 1 hour the solution was colourless. After filtration it was evaporated to small volume and poured on to ice. 4-Acetamino-carvacrol rapidly crystallized as a white solid, recrystallized from 30% alcohol, m.p. 180-181°. λMax. 280 mμ (logε, 3.35). This phenol, like the parent carvacrol, gave no characteristic ferric chloride colouration.

Acetylation of 4-acetamino-carvacrol - (a) 4-Acetamino-carvacrol (52 mg.) was dissolved in 2N sodium hydroxide solution and cooled to 0°. Addition of acetic anhydride dropwise, until the mixture was just acid, gave a white solid (55 mg.) which on recrystallization from petrol-ethyl acetate (2:1) gave 4-acetamino-carvacryl acetate (26) as white needles, m.p. 161-162°. λmax. 273 mμ (logε, 3.01). (b) 4-Acetamino-carvacrol was refluxed in acetic anhydride for 1 hour. The product which crystallized on pouring on to

crushed ice was the triacetyl-derivative (27). M.p. 73-74°, white needles from petrol (b.p. 40-60°). $\nu_{max.}^{KCl}$ 1755, 1705, 1580, 1500, 920, 790. $\nu_{max.}^{CCl_4}$ 1760, 1705 cm.$^{-1}$ λmax. 266 mμ (log ε, 2.96); 274 mμ (log ε, 2.93). (Found: C, 66.16; H, 7.05; N, 4.97. $C_{16}H_{21}O_4N$ requires C, 65.95; H, 7.27; N, 4.81%).

The effect of ethanolic sulphuric acid on carenodione (10) - Carenedione (1.18 g.) was refluxed for 4 hours under nitrogen in ethanol (20 ml.) containing concd. sulphuric acid (1.0 ml.). At the end of this time the dark red solution was partially evaporated, and the product isolated by pouring into water, and extraction with benzene. The crude brown oil obtained on evaporation smelled distinctly phenolic, and showed -OH and aromatic bands in the infra-red (3400s, 1620 m, 1510s cm.$^{-1}$). This material distilled as a reddish liquid, b.p. 100-106°/0.1 mm., n_D^{21} 1.5279. Repeated distillations, under nitrogen, failed to yield a colourless distillate. νmax. 3350s, 1605 m, 1500s, 1205s, 1050s, 860 m.cm.$^{-1}$ λmax. (EtOH) 225 mμ (log ε, 3.65)*; 292 mμ (log ε, 3.36)*. λmax. (KOH in EtOH) 238 mμ (log ε, 3.78)*; 307 mμ (log ε, 3.41)*. (* log ε values calculated on basis of M.W. 124). (Found: C, 70.01; H, 8.76. $C_7H_8O_2$ (33a) requires C, 67.75; H, 6.46%. $C_{12}H_{18}O_3$ (33b) requires C, 68.58; H, 8.57%).

Chromatography of this compound, or mixture of compounds, on silica gel did not lead to any less highly coloured product, nor to the production of any crystalline material.

The rearrangement product was soluble in 4N sodium hydroxide. Addition of benzoyl chloride or acetic anhydride to the alkaline solution yielded no crystalline derivative. The phenol gave no characteristic colour with ferric chloride.

Attempts to form solid derivatives of the hydroxy-compound with the usual reagents, such as α-naphthyl isocyanate and p-bromobenzenesulphonyl chloride, were unsuccessful. The compound slowly decolourized bromine water, but gave no solid product.

The rearrangement product was refluxed for 1 hour with chloroacetic acid in the presence of sodium hydroxide solution. Acidification, extraction with ether and sodium carbonate re-extraction of the ether layer gave on acidification of the sodium carbonate extract, a pale brown solid in only 10% yield. Recrystallization of this material (four times) from carbon tetrachloride gave a derivative as white prisms, m.p. 111°. (Found: C, 62.50; H, 6.61%).

When the crude hydroxy-compound (300 mg.) was refluxed with zinc dust in a 1:1 mixture of acetic acid-acetic anhydride for 30 mins., the product isolated by pouring into water and extraction with benzene in the usual way, was a pale yellow liquid (400 mg.), b.p. 120°/0.8 mm., n_D^{20} 1.5062. $\nu_{max.}^{CCl_4}$ 3570 vw, 3480 w, 1750 vs, 1703 m, 1316 m, 1180 vs, 1118 s $cm.^{-1}$ λmax. 278.5 mμ (log ε, 3.31). (Found: C, 69.16; H, 7.61. $C_{12}H_{16}O_3$(?) requires C, 69.21; H, 7.74%).

A small sample of the hydroxy-compound was oxidized by chromium trioxide in acetone. The usual processing gave a crude carbonyl compound, which was treated with a methanolic hydrochloric acid solution of 2:4-dinitrophenyl-hydrazine. A brick-red derivative was obtained in the form of needles, m.p. 128°, after recrystallization from methanol. λmax. ($CHCl_3$) 413 mμ (log ε, 4.40). (Found: C, 55.93; H, 5.11; N, 14.15. $C_{18}H_{20}O_6N_4$ (36) requires

C, 55.66; H,5.19; N,14.43%)

(The 2:4-dinitrophenylhydrazone of carenedione is a scarlet solid, m.p. >300°(dec.), insoluble in boiling methanol or chloroform).

On repeating the above oxidation on a rather larger scale, an attempt was made to isolate any quinonoid product by sublimation. A beautiful yellow solid sublimed at 30-40°/0.25 mm. The yield was quite low, being less than 20%. Resublimation gave yellow needles, m.p. 66° λmax. 247 mμ (log ε,4.05); 315 mμ (log ε,2.78). (Toluquinone (37) has m.p. 69°, λmax. 248 mμ (log. ε,4.1); 316 mμ (log ε,2.7). (Found: C, 68.34; H,5.05, $C_7H_6O_2$ requires C, 68.84; H, 4.95%).

The material which sublimed at temperatures greater than the above yellow compound consisted largely of a dark brown tar, with a complex infra-red spectrum, which was not farther investigated.

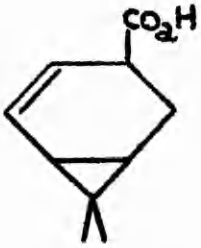
Irradiation of carenedione (10) - (a) Carenedione (720 mg.) in ethanol (100 ml.) was irradiated by means of a 100 watt mercury lamp. The solution was contained in a quartz flask, and the experiment was conducted under nitrogen, at the temperature of the refluxing solvent. The reaction could be followed by withdrawing aliquots at suitable intervals, and observing the changes in ultra-violet absorption. After 21 hours, the high-intensity absorption band at 246 mμ had disappeared, and indeed, the product was transparent in the ultra-violet above 210 mμ. The solvent was evaporated and the crude product dissolved in benzene and chromatographed on silica. (Neutral alumina led to the decomposition of most of the product). The main product

appeared to be an ester, b.p. 65°/0.07 mm. n_D^{20} 1.4828. νmax. 1760, 1720, 1645 cm.$^{-1}$ (Found: C, 71.08; H,8.40. $C_{14}H_{20}O_3$ (?) requires C, 71.16; H, 8.53%).

(b) Carenedione was irradiated under the conditions already described, in 90% dioxan for 24 hours. The product, isolated along with unreacted carenedione (25%), by chromatography on silica, was a viscous liquid, almost a glass, b.p. 120°/0.08 mm. νmax. 3500 m, 1770 m, 1685 vs cm.$^{-1}$ No ultra-violet absorption above 210 mμ (Found: C,65.00; H, 7.84. $C_{10}H_{14}O_3$ requires C, 65.91; H 7.74%)

The product did not appear to be acidic, and in fact was recovered unchanged from a solution of diazo-methane.

Attempts to form solid derivatives of the irradiation product with α-naphthyl isocyanate and 3-nitro-phthalic anhydride were unsuccessful. The hydroxy-compound was recovered unchanged from treatment with excess chromium trioxide solution in acetone. It appeared to decompose rapidly when treated with cold 4N sodium hydroxide.



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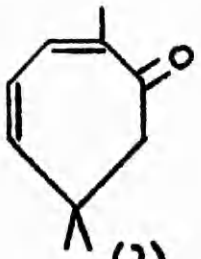

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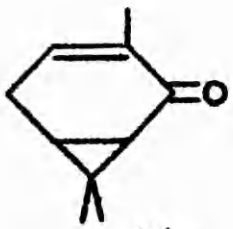

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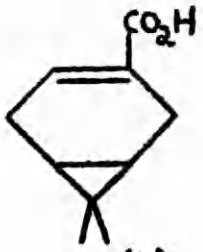

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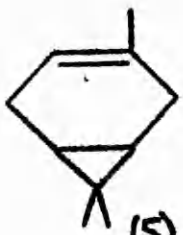

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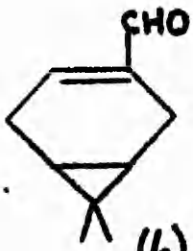

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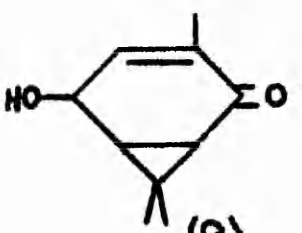

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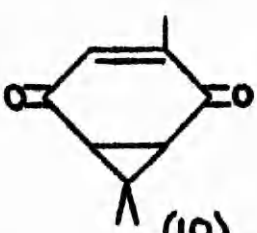

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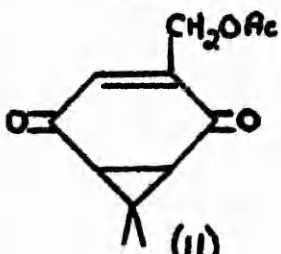

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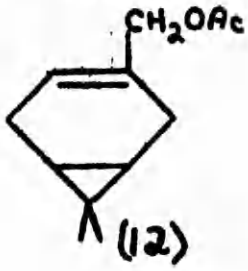

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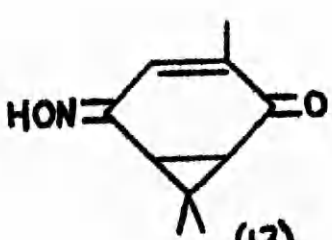

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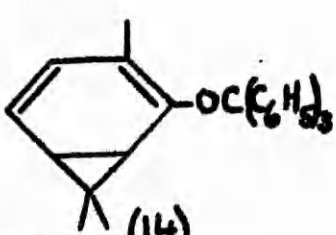

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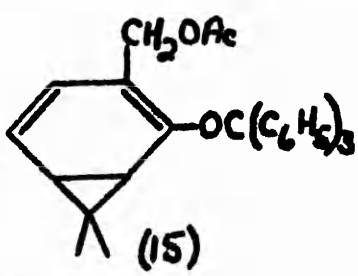

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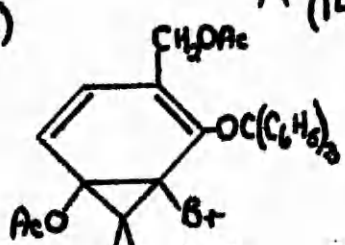

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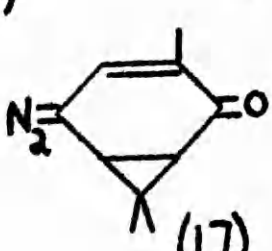

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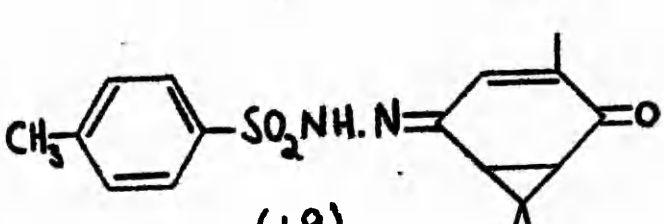

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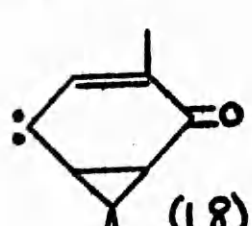

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SUMMARY OF Ph.D. THESIS

IAN WILLIAM JAMES STILL

STUDIES IN THE CYCLOHEPTANE FIELD

In Section I, some of the reactions of tropilidene (or cycloheptatriene) are described. Attempts to convert tropilidene directly into tropone, or the so far unknown tropyl alcohol, by employing a variety of common oxidative procedures, have been unsuccessful. Active manganese dioxide, sodium dichromate, and performic acid all led to the formation of benzaldehyde in varying amounts. Attempts to epoxidize tropilidene, using monoperphthalic, perbenzoic, and performic acids, have likewise met with no success.

The latter part of Section I deals with the evidence obtained for the structures of the previously described bromine and hydrogen bromide addition products of tropilidene. In both cases it seems likely that a 1,2-addition mechanism is involved. Attempts to prepare hypobromous acid and ethyl hypobromite addition products were not successful - considerable amounts of benzaldehyde being produced in each case.

In Section IIa, synthetic work is described, which establishes the nature of the dehydration product of 2-hydroxy-2,6,6-trimethylcyclohept-4-en-1-one. This hydroxy-ketone was obtained previously as a product of the selenium dioxide oxidation of α-dihydroeucarvone. Ring-contraction occurs on dehydration with the formation of 1-acetyl-5,5-dimethylcyclohexa-1,3-diene. This ketone

has been synthesized from 5,5-dimethylcyclohexan-1,3-dione (dimedone), while its tetrahydro-derivative, 1-acetyl-3,3-dimethylcyclohexane, has also been synthesized from 3-methylcyclohex-2-en-1-one.

A number of oxidative degradations are also described in Section IIa, with a view to establishing the position of the double bond in α-dihydroeucarvone. These experiments were inconclusive, but the results of isomerizations to the conjugated β-dihydroeucarvone, in conjunction with the evidence obtained by vapour phase chromatography, indicated that α-dihydroeucarvone is in fact a mixture containing 75% of the $\gamma\delta$-unsaturated ketone, and 25% of the $\beta\gamma$-unsaturated ketone. This conclusion is confirmed by the nuclear magnetic resonance data.

A dimeric product, or mixture of products, obtained by the action of alkali on eucarvone is briefly described.

In Section IIb, the conversions of eucarvone into carenedione, and eucarvone trityl enol-ether are described. Various attempts to oxidize these bicyclic derivatives, with a view to the synthesis of the naturally occurring monoterpene, chamic acid, were unsuccessful.

Oximino-eucarvone, or carenedione monoxime, was converted to the corresponding diazo-ketone, which underwent thermal isomerization in the presence of air to yield carenedione. No useful results were obtained from attempted Beckmann rearrangements of oximino-eucarvone, but this compound yielded interesting iso-oxazoline rearrangement products on treatment with sulphuric acid. The structures of

these products have been fully elucidated by hydrogenolytic cleavage to known derivatives of carvacrol. Some interesting features of the ultra-violet absorption spectra of the rearrangement products and their derivatives are discussed.

Finally, the action of hot dilute acid on carenedione has afforded a rearrangement product, which may be a mixture of two hydroquinone derivatives. The evidence so far obtained for the two structures is discussed. The irradiation of carenedione yielded what appeared to be a hydroxy-lactone, but very little evidence has been obtained for its structure.